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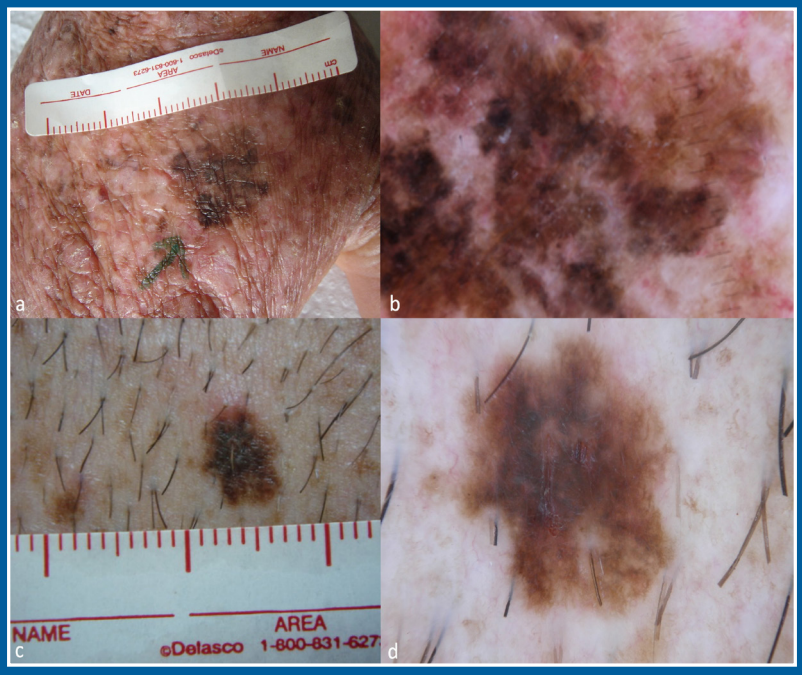

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CONTENTS

Original Article

Human Papillomavirus (HPV) Awareness and Vaccine Hesitancy Among Medical Students: A Cross-Sectional Study on Knowledge, Stigma, and Preventive Behavior

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Abstract

Aim: Human papillomavirus (HPV) is a leading cause of several anogenital and oropharyngeal cancers, yet vaccination rates remain suboptimal globally. In addition to limited access and cost-related barriers, stigma surrounding HPV can hinder vaccine uptake and preventive health behavior. This study aimed to evaluate HPV-related knowledge, attitudes, and perceived stigma among medical students, and to identify key factors influencing vaccine acceptance.

Materials and Methods: A descriptive cross-sectional survey was conducted among 220 medical students. Participants completed a structured questionnaire including socio-demographic items, HPV Knowledge Scale, and questionnaires assessing vaccination attitudes and HPV-related stigma. Statistical analyses included chi-square, t-tests, analysis of variance, and correlation analysis.

Results: The mean age of participants was 22.6±1.3 years; 63.6% were female. Although overall HPV awareness was high, only 19.1% had received at least one dose of the vaccine. Cost was the most cited barrier (40.9%), and 65% indicated willingness, to be vaccinated, if the vaccine were free. Students with prior sexual experience were more likely to be vaccinated ($P = 0.043$). Knowledge scores increased with academic year ($P < 0.05$). A negative correlation was observed between knowledge and stigma scores ($r = -0.238$, $P < 0.001$). Nearly half reported they would feel shame or guilt if diagnosed, and 76% expressed concerns about the infection's impact on relationships. No significant gender differences were found in stigma.

Conclusion: Despite high awareness, persistent stigma remains among future healthcare providers, suggesting that medical education alone may be insufficient. Integrating value-sensitive, culturally informed content into medical training-alongside policy interventions to address vaccine affordability may be essential in reducing stigma and improving vaccination.

Keywords: Papillomavirus infections, papillomavirus vaccines, medical students, social stigma, vaccine hesitancy, cross-sectional studies

Introduction

Human papillomavirus (HPV) is one of the most common sexually transmitted infections (STIs) worldwide, affecting millions of individuals across diverse populations and age groups. Among over 100 known genotypes, low-risk types such as HPV-6 and HPV-11 are linked to benign conditions like genital warts, whereas high-risk types-particularly HPV-16 and HPV-18-are strongly associated with cervical, anal, and oropharyngeal cancers.[1]

Cervical cancer remains a significant public health concern, particularly in low- and middle-income countries, which account for over 80% of global cases and deaths due to limited access to screening and preventive care.[1,2] Persistent infection with high-risk HPV types is recognized as the primary cause of nearly all cervical cancer cases.[3,4]

The availability of prophylactic HPV vaccines-such as the bivalent (Cervarix®), quadrivalent (Gardasil®), and the more

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recent nonavalent vaccine (Gardasil 9®), which provides protection against nine HPV types (6, 11, 16, 18, 31, 33, 45, 52, and 58) offers strong protection against the most oncogenic HPV types.[2,5] Despite robust evidence supporting the efficacy and safety of HPV vaccines-with up to 100% protection against cervical intraepithelial neoplasia in HPV-naive individuals-the global coverage of HPV vaccination remains disappointingly low.[4] Factors such as socio-economic disparities, lack of awareness, cultural resistance, perceived stigma surrounding HPV and concerns regarding vaccine safety pose major barriers to widespread vaccine implementation, particularly in regions with high disease burden.[3,6-9]

Medical students, as future healthcare professionals, represent a crucial group in shaping public health outcomes. However, several studies suggest that even among medical students, knowledge and attitudes toward HPV vary considerably, often reflecting gaps in formal education and public discourse.[10,11] In addition, individuals may internalize feelings of shame, guilt, or fear of judgment associated with a potential HPV diagnosis.[7,10]

This study aims to evaluate medical students' knowledge, attitudes, and stigma perceptions regarding HPV and HPV vaccination. By identifying the extent of awareness and exploring potential barriers to vaccine acceptance in this population, the findings of this study may contribute to the refinement of educational strategies within medical curricula and support future health promotion efforts.

Materials and Methods

Study Design and Participants

This descriptive cross-sectional study was conducted from February to April 2025 at Demiroğlu University Faculty of Medicine, Department of Dermatology and Venereology. The study population included medical students from all academic years (1st to 6th year). According to the university records, a total of 480 students were enrolled in the 2024-2025 academic year. Using a 95% confidence level and a 5% margin of error, the minimum required sample size was calculated as 214 students. Ultimately, 220 students who agreed to participate and completed the survey in full were included in the final analysis. Inclusion criteria consisted of currently enrolled medical students who voluntarily agreed to participate, and provided informed consent. Students who failed to complete the questionnaire or declined participation were excluded. The study received approval from the Ethics Committee of Demiroğlu University (approval number: 51016662/44718, date: 26.02.2025). Written informed consent was obtained from all participants prior to data collection.

Measurement Tools

The study employed a structured, face-to-face questionnaire composed of four main sections.

Socio-demographic Questionnaire

This section collected data on participants' age, gender, academic year, and history of sexual activity.

HPV Knowledge Scale (HPV-KS)

The HPV Knowledge Scale (HPV-KS) was originally developed by Waller et al.[12] to assess individuals' factual knowledge regarding HPV, including its modes of transmission, associated diseases, risk factors, and preventive strategies. The scale was subsequently translated and psychometrically validated for use in the Turkish population by Bozkurt and Özdemir[13] The Turkish version of the scale comprises 33 items, each rated as true, false, or don't know. Each correct response is scored as 1, while incorrect or uncertain responses receive 0 points; yielding a total score range from 0 to 33. Higher scores reflect a greater level of knowledge about HPV. The Turkish adaptation has demonstrated acceptable reliability and content validity (Cronbach's alpha > 0.80), making it a suitable instrument for assessing HPV-related knowledge among Turkish-speaking populations.[13]

HPV Vaccination Attitudes Questionnaire

This section, developed by the researchers based on a review of prior literature on HPV vaccination behaviors and attitudes, assessed participants' awareness and perceptions regarding HPV and the HPV vaccine, along with their self-reported vaccination status.[14-17]

HPV-Related Stigma Questionnaire

Developed by the researchers based on existing literature, this scale evaluates stigmatizing beliefs and attitudes toward individuals with HPV infection or those who receive the HPV vaccine.[7,8,14,18-22] The scale consists of 15 items rated on a five-point Likert scale ranging from "strongly disagree" to "strongly agree."

Statistical Analysis

All data were analyzed using IBM SPSS Statistics version 23. Descriptive statistics (means, standard deviations, frequencies, and percentages) were used to summarize participants' characteristics. The Shapiro-Wilk test was applied to assess the normality of continuous variables. Chi-square tests were used for comparisons between categorical variables.

For continuous variables, independent samples t-tests were used for normally distributed data, while the Mann-Whitney U test was applied for non-parametric data. One-way analysis of variance (ANOVA) was used to compare mean knowledge scores across academic years when assumptions of homogeneity were met. In cases where variance homogeneity could not be assumed, Welch's ANOVA was applied. For post hoc comparisons, Tukey's test was used when variances were equal, and the Games-Howell test was employed when variances were unequal. A *P* value of < 0.05 was considered statistically significant.

Results

A total of 220 medical students participated in the study. The mean age was 22.6±1.3 years. The study population consisted of 63.6% female (n = 140) and 36.4% male (n = 80) students. When the academic year was considered, 17.3% were in their sixth year (n = 38), followed by 28.2% in the fifth year (n = 62), 15.9% in the fourth year (n = 35), 14.1% in the third year (n = 31), 9.1% in the second year (n = 20), and 15.5% in the first year (n = 34). Regarding marital status, 99.5% of participants (n = 219) reported being single, while only 0.5% (n = 1) stated they were married.

As for sexual experience, 50.0% (n = 110) reported having prior sexual experience, 33.6% (n = 74) reported no sexual experience, and 16.4% (n = 36) preferred not to disclose this information. A statistically significant association was found between sexual experience and HPV vaccination status, with participants who reported prior sexual experience being more likely to have received the HPV vaccine ($\chi^2 = 6.28$, $P = 0.043$).

Regarding HPV vaccination, 19.1% of participants (n = 42) reported having received the HPV vaccine, 64.5% (n = 142) stated they had not been vaccinated, and 16.4% (n = 36) indicated that they were considering getting vaccinated in the future. Among all participants, 15.5% (n = 34) reported receiving the full three-dose HPV vaccine series, while 2.3% (n = 5) had received two doses and 1.4% (n = 3) had received only one dose.

In terms of perceived barriers to vaccination, which were presented in Figure 1, cost was the most frequently cited obstacle, reported by 40.9% of participants. When asked about their primary sources of information on HPV, 69.1% (n = 152) of participants reported medical school courses as a source, followed by 26.8% (n = 59) who cited internet or social media, 23.2% (n = 51) who mentioned healthcare professionals, 11.4% (n = 25) who learned from friends or family, and only 1.4% (n = 3) who obtained information from TV or print media.

As shown in Table 1**,** most participants considered HPV a serious health concern and believed in the effectiveness of HPV vaccination. However, a substantial portion (11.4%) expressed concerns about receiving the vaccine, primarily due to potential side effects or safety issues. Additionally, approximately two-thirds (65.0%) indicated they would be willing to get vaccinated if it were provided free of charge.

HPV-KS results, which assess students' knowledge levels, are shown in Table 2. Female students scored significantly higher than males in the HPV testing knowledge section (*P* = 0.003), while no significant differences were observed in other domains. As shown in Table 3, total HPV-KS scores and all subscale scores increased progressively with academic year. Students in higher academic years, particularly from the 3rd year onward, demonstrated significantly greater HPV-related knowledge compared to those in the 1st and 2nd years

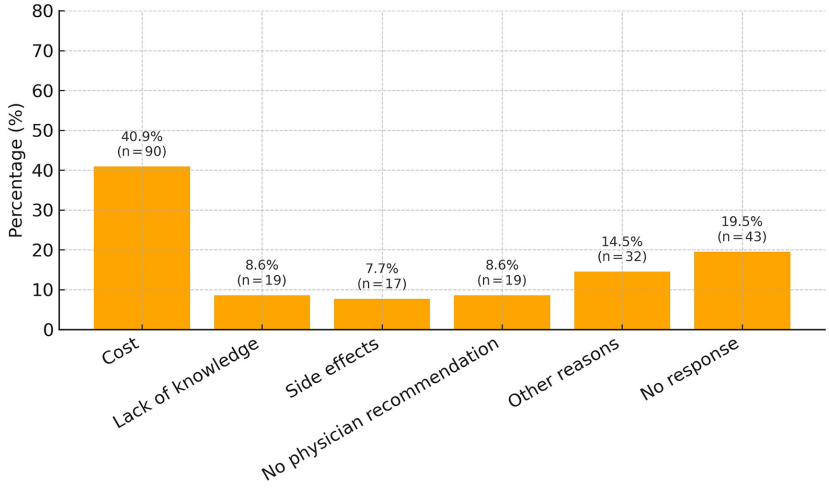

Figure 1. Perceived barriers to HPV vaccination
HPV: Human papillomavirus

($P < 0.05$). Post hoc comparisons, (Games-Howell or Tukey tests) indicated that the 1st and 2nd year students formed a statistically distinct group with lower knowledge scores, while the 6th year students consistently had the highest scores across all domains.

As summarized in Table 4, stigmatizing beliefs related to HPV were common. Nearly half of the students (46.8%) reported that a positive HPV status would cause feelings of guilt, and 76.3% believed it could negatively impact romantic relationships. Furthermore, 77.3% stated they would avoid a relationship with someone diagnosed with HPV. Social stigma was also apparent, as 34.6% perceived individuals with HPV as sexually irresponsible, 43.7% believed that a person with HPV is socially stigmatized, and 5.9% reported they would hesitate to disclose an HPV diagnosis to their physician. Statistical analysis revealed no significant gender-based differences in participants' responses to the HPV stigma and social perception items, indicating similar levels of perceived stigma among both male and female students. A total stigma score was calculated by summing all 15-item responses on the HPV stigma scale, with response options scored from 1 (strongly disagree) to 5 (strongly agree). A statistically significant negative correlation was found between HPV-KS scores and total stigma scores ($r = -0.238$, $P < 0.001$), suggesting that participants with higher levels of HPV knowledge tended to exhibit lower levels of stigma.

Table 1. Attitudes and awareness towards HPV and HPV vaccination

Statement	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
HPV is a serious health problem	2.3% (n = 5)	2.7% (n = 6)	5.0% (n = 11)	22.7% (n = 50)	67.3% (n = 148)
I believe HPV vaccination is effective in preventing cancer	2.3% (n = 5)	1.8% (n = 4)	9.5% (n = 21)	21.4% (n = 47)	65.0% (n = 143)
It is recommended that the HPV vaccine should also be administered to males	3.2% (n = 7)	1.4% (n = 3)	8.2% (n = 18)	29.1% (n = 64)	58.2% (n = 128)
I feel concerned about receiving the HPV vaccine (e.g., side effects, safety)	39.5% (n = 87)	30.5% (n = 67)	18.6% (n = 41)	9.1% (n = 20)	2.3% (n = 5)
I would get the HPV vaccine if it were free	1.4% (n = 3)	2.7% (n = 6)	11.4% (n = 25)	21.4% (n = 47)	43.6% (n = 96)

HPV: Human papillomavirus

Table 2. Comparison of HPV knowledge scale scores by gender

HPV-KS	Female (mean ± SD)	Male (mean ± SD)	*P* value
General HPV knowledge (16 items)	12.15±2.43	11.82±3.13	0.397
HPV testing knowledge (6 items)	3.31±1.61	2.62±1.68	0.003
HPV vaccination knowledge (7 items)	5.09±1.63	4.87±1.75	0.364
HPV vaccine availability (4 items)	1.94±1.02	1.76±1.08	0.212
Total HPV-KS score (33 items)	22.48±5.47	21.06±6.19	0.083

HPV-KS: Human Papillomavirus-Knowledge Scale, SD: Standard deviation

Table 3. Comparison of HPV knowledge scale scores by academic year

Academic year	General HPV knowledge (mean ± SD)*	HPV test knowledge (mean ± SD)**	HPV vaccination knowledge (mean ± SD)*	HPV vaccine availability (mean ± SD)**	total HPV-KS score (mean ± SD)*
1st year	8.94±3.66^{a}	1.82±1.64^{a}	3.71±1.96^{ab}	1.03±1.11^{a}	15.50±6.95^{a}
2nd year	9.35±2.66^{a}	2.10±1.83^{a}	2.95±2.19^{a}	1.05±1.00^{a}	15.45±6.23^{a}
3rd year	12.26±1.41^{b}	2.61±1.43^{ab}	5.06±1.55^{b}	2.06±0.81^{b}	22.00±3.60^{b}
4th year	12.66±1.53^{b}	3.31±1.23^{bc}	5.46±1.04^{b}	2.06±0.80^{b}	23.49±2.63^{b}
5th year	13.10±1.43^{b}	3.45±1.41^{bc}	5.60±1.09^{b}	2.35±0.87^{b}	24.50±3.21^{bc}
6th Year	13.79±1.26^{b}	4.08±1.60^{c}	5.76±1.08^{b}	1.97±1.00^{b}	25.61±3.61^{c}

Different superscript letters ($^{a, b, c}$) indicate statistically significant differences between academic years. Groups that share the same letter are not significantly different from each other ($P < 0.05$; *Games-Howell or **Tukey post hoc tests).
HPV: Human papillomavirus, SD: Standard deviation, KS: Knowledge scale

Table 4. Perceived stigma and social attitudes toward HPV infection

Item statement	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
If I tested positive for HPV, I would feel contaminated	13.2% (n = 29)	15.9% (n = 35)	21.8% (n = 48)	30.9% (n = 68)	18.2% (n = 40)
Being HPV positive would be shameful for me	15.0% (n = 33)	23.6% (n = 52)	21.8% (n = 48)	25.9% (n = 57)	13.6% (n = 30)
I would feel guilty if I tested positive for HPV	10.9% (n = 24)	22.7% (n = 50)	19.5% (n = 43)	32.3% (n =71)	14.5% (n = 32)
Being diagnosed with HPV would lower my self-esteem	11.8% (n = 26)	14.5% (n = 32)	22.3% (n = 49)	35.9% (n = 79)	15.5% (n = 34)
If I had an HPV infection, I would be worried about having a relationship	1.8% (n = 4)	2.7% (n = 6)	10.0% (n = 22)	44.5% (n = 98)	40.9% (n = 90)
A person diagnosed with HPV is seen as sexually irresponsible	6.8% (n = 15)	32.7% (n = 72)	25.9% (n = 57)	25.5% (n = 56)	9.1% (n = 20)
Most people would avoid romantic relationships with someone who is HPV positive	0.5% (n = 1)	6.4% (n = 14)	16.8% (n = 37)	53.6% (n = 118)	22.7% (n = 50)
I would avoid a relationship with someone who has HPV	0.5% (n = 1)	4.5% (n = 10)	17.3% (n = 38)	37.3% (n = 82)	40.0% (n = 88)
A person with HPV is socially stigmatized	6.4% (n = 14)	22.3% (n = 49)	27.3% (n = 60)	31.4% (n = 69)	12.3% (n = 27)
I would not mind being friends with someone who has HPV	1.8% (n = 4)	5.9% (n = 13)	18.2% (n = 40)	35.0% (n = 77)	38.6% (n = 85)
Doctors and nurses treat people with HPV differently	27.3% (n = 60)	30.5% (n = 67)	19.5% (n = 43)	14.5% (n = 32)	8.2% (n = 18)
Undergoing testing for HPV might lead people to question my sexual history	15.5% (n = 34)	21.4% (n = 47)	15.9% (n = 35)	33.6% (n = 74)	13.6% (n = 30)
A diagnosis of HPV would reduce my chances of having a good marriage in the future	12.7% (n = 28)	23.6% (n = 52)	28.6% (n = 63)	23.6% (n = 52)	11.4% (n = 25)
People assume that those who get vaccinated for HPV are sexually active	20.9% (n = 46)	22.3% (n = 49)	11.8% (n = 26)	34.1% (n = 75)	10.9% (n = 24)
I would hesitate to tell my doctor if I tested positive for HPV	64.5% (n = 142)	22.7% (n = 50)	6.8% (n = 15)	3.6% (n = 8)	2.3% (n = 5)

HPV: Human papillomavirus

Discussion

This study explored medical students' knowledge, attitudes, and perceived stigma related to HPV and HPV vaccination. This approach highlights how medical education, personal experience, and sociocultural context intersect to shape perceptions of HPV-related behaviors. The findings revealed that despite high levels of awareness, stigma remains prevalent and may influence vaccine hesitancy. Knowledge scores increased with academic year, and higher knowledge was associated with lower stigma. These results suggest that factual knowledge alone may be insufficient to combat stigma, emphasizing the need for early, value-sensitive education. Additionally, cost was reported as the most frequently cited barrier to vaccination, underscoring the need for improved accessibility. Importantly, unlike previous research, our study assessed the relationship between HPV knowledge, stigma, and sexual experience**,** offering a more comprehensive view of the behavioral factors influencing vaccine acceptance.

In this context, personal sexual history emerged as a significant factor influencing vaccination behavior, with participants who had prior sexual experience being significantly more likely to have received the HPV vaccine. This likely reflects a greater perceived vulnerability to infection after sexual debut-a trend supported by prior research showing that sexual experience often motivates vaccine-seeking behavior.[23,24] However, despite this association, the overall vaccination rate in our sample remained low (19.1%), echoing global evidence that vaccine uptake among medical students is often suboptimal.[25,26] These findings emphasize the importance of initiating vaccination before sexual activity and developing preventive strategies that go beyond knowledge, including reducing vaccine costs, addressing stigma, and enhancing accessibility.[8,17,25]

HPV-related awareness was consistently high across recent studies conducted in Türkiye; however, vaccination rates remained low. While prior studies reported HPV vaccine uptake rates of 3.5% and 7.5%, our study found a notably

higher rate of 19.1%, which may reflect regional or institutional differences in access, education, or vaccine promotion strategies.[27-29] Despite this difference, the most frequently cited obstacle to vaccination was cost (40.9%), which aligns with both national and international findings that financial burden is a significant deterrent to vaccination[7,15,17,27,30] In a recent systematic review by Zheng et al.[7], more than two-thirds of studies (9/13) reported that the cost of vaccines was a concern in both developed and developing countries. Reflecting this concern, nearly two-thirds of our participants (65%) indicated a willingness to be vaccinated if the vaccine were provided free of charge or covered by their health insurance, underscoring the pivotal role of affordability in vaccination decisions. In many contexts, the lack of insurance coverage for the HPV vaccine has also been identified as a structural barrier that limits equitable access.[16,31]

Concerns about adverse effects have been consistently identified in the literature as one of the leading causes of HPV vaccine hesitancy.[7,8,16] Although such fears are widespread in the general population, only 11.4% of participants in our study expressed concerns about vaccine safety in general, and just 7.7% specifically cited side effects or safety concerns as a direct barrier to receiving the HPV vaccine. This relatively low proportion is likely influenced by participants' medical education, which provides more reliable and evidence-based information, thereby reducing susceptibility to misinformation and vaccine-related anxiety.

Our findings revealed that although overall HPV knowledge scores did not significantly differ by gender, female students scored significantly higher than male students in the "HPV Testing Knowledge" domain, which includes items related to the function, timing, and interpretation of HPV testing procedures. This discrepancy may be partly attributed to the fact that HPV screening guidelines and cervical cancer prevention efforts predominantly target women, resulting in greater exposure to such information among female students. Previous studies have shown that women are more likely to receive information on HPV testing during gynecological visits or through public health campaigns, which may further contribute to this gender-based knowledge gap.[21,32,33] Our findings revealed a significant increase in HPV knowledge with academic year, particularly among 5th and 6th year students. This aligns with recent studies reporting higher HPV awareness among senior medical students, likely due to greater clinical exposure and structured curriculum content.[25,26] Targeted educational interventions have been shown to improve HPV knowledge, especially in earlier academic years, where baseline understanding tends to be lower.[23] These results highlight the need to introduce comprehensive HPV education earlier in medical training to reduce knowledge gaps and support preventive health efforts.

A considerable proportion of participants exhibited stigmatizing beliefs or social concerns regarding HPV infection. For example, nearly half of the students agreed or strongly agreed that testing positive for HPV would evoke feelings of shame or guilt, while 51.4% believed that being diagnosed would lower their self-esteem. These findings align with previous studies indicating that HPV-related stigma may stem from its sexual transmission route, contributing to internalized guilt and fear of social judgment.[11,21,22,32]

Relational concerns were also prominent; 76.3% of participants reported that having HPV would make them worry about forming romantic relationships, and 77.3% said they would avoid being in a relationship with someone who has HPV. These high levels of interpersonal stigma underscore how infection status may influence students' social and emotional wellbeing. Moreover, 34.6% agreed that people with HPV are perceived as sexually irresponsible, and 47.2% believed others would question their sexual history if they themselves got tested. These attitudes indicate that, despite medical training, HPV continues to be viewed not solely as a medical issue but also as a reflection of moral character-mirroring broader societal narratives that link STIs with moral judgments.[8,16,25] Notably, the Ziaee et al.[21] study contributes a critical nuance: while higher knowledge about HPV is often assumed to reduce stigma, their data revealed that knowledge does not always translate to more accepting attitudes. In fact, some forms of partial knowledge-particularly in domains like transmission or recurrence-were associated with increased levels of stigma. This counterintuitive pattern highlights a critical gap in HPV education: factual knowledge alone may not suffice to reduce stigma unless accompanied by value-sensitive content that challenges moralistic assumptions.

Gender remains a complex dimension in shaping perceptions of HPV-related stigma. Interestingly, despite well-documented gender disparities in public perceptions of HPV, which often disproportionately target women with greater stigma, our findings revealed no significant difference in stigma levels between male and female students.[9,34,35] This uniformity may be attributed to participants' medical education, which likely fosters a shared biomedical framework that tempers gendered moral judgments. It is possible that exposure to standardized scientific discourse reduces the influence of sociocultural stereotypes that typically associate HPV with female promiscuity or shame. Nevertheless, the persistence of stigma across both genders in a medically educated population underscores the depth of implicit societal narratives surrounding STIs. Despite participants' medical training, the high levels of stigma observed may reflect broader sociocultural norms in Türkiye, where discussions of sexuality and STIs are often influenced by traditional values, modesty, gender expectations, and patriarchal ideologies.

These cultural dynamics may reinforce shame and secrecy around HPV, even within clinical contexts.

These entrenched beliefs are concerning because they can interfere with public health efforts to promote HPV vaccination and routine screening. Research consistently shows that stigma serves as a barrier to preventive behaviors, including vaccine uptake and early diagnosis.[21,32] The internalized shame and fear of judgment may lead individuals to avoid healthcare contact altogether, even when services are available and free. Given that the HPV vaccine has not yet been incorporated into the national immunization schedule in Türkiye, understanding medical students' perspectives is especially valuable for anticipating and guiding future public health efforts. It prepares future physicians to effectively communicate with patients and counteract misinformation or stigma once the vaccine becomes widely available. Equipping future physicians with accurate knowledge may not only influence their clinical practice but also improve the success of forthcoming public vaccination campaigns.

Therefore, combating HPV stigma requires more than medical information. It calls for value-sensitive health communication, structural interventions to ensure confidential and nonjudgmental services, and the integration of stigma-reduction modules into medical curricula. Especially in training institutions, fostering empathy and challenging moralistic narratives around STIs is crucial to shaping future healthcare professionals' attitudes and behaviors.

Study Limitations

This study has several limitations to consider. First, as data were collected from medical students at a single institution, the findings primarily reflect the perspectives of this specific academic context and may not capture variability across other institutions. Second, the reliance on self-reported data could have introduced response biases, particularly on sensitive topics such as sexual experience, stigma, and vaccination status. Third, the cross-sectional nature of the study limits causal interpretations between HPV knowledge, stigma, and vaccination behavior. Lastly, although the HPV-related stigma scale was developed based on literature and expert input, it has not undergone formal psychometric validation, which may affect its comparability to other standardized tools.

Conclusion

This study highlights the persistence of HPV-related stigma and vaccine hesitancy among medical students, despite high levels of awareness and formal education. Although overall knowledge scores were satisfactory, stigma remained prevalent, indicating that scientific training alone may be insufficient to counteract deep-rooted sociocultural narratives. The observed negative correlation between HPV knowledge and stigma further underscores the importance of integrating not only factual content but also value-based discussions into medical curricula. Cost, safety concerns, and limited access emerged as key barriers to vaccination, suggesting the need for policy-level interventions to increase vaccine availability and affordability. Ultimately, empowering future healthcare professionals with both factual knowledge and empathetic understanding may be key to breaking down HPV-related stigma and improving vaccine acceptance.

Ethics

Ethics Committee Approval: The study received approval from the Ethics Committee of Demiroğlu University (approval number: 51016662/44718, date: 26.02.2025).

Informed Consent: Written informed consent was obtained from all participants prior to data collection.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.A.Y., T.N.K., Concept: E.A.Y., Design: E.A.Y., T.N.K., Data Collection or Processing: E.A.Y., T.N.K., Analysis or Interpretation: E.A.Y., T.N.K., Literature Search: E.A.Y., T.N.K., Writing: E.A.Y., T.N.K.

Conflict of Interest: The authors declared that they have no conflict of interest.

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Original Article

Benchmarking Large Language Models on the Turkish Dermatology Board Exam: A Comparative Multilingual Analysis

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Abstract

Aim: Large language models (LLMs) are increasingly integrated into medical education; however, their performance on dermatology examinations in non-English contexts has not been extensively studied. This study aimed to evaluate the performance of six LLMs in terms of accuracy, error profile, and response time on the Turkish Dermatological Society (TDS) qualifying examination.

Materials and Methods: Two hundred publicly available multiple-choice questions from the TDS exam were submitted to six LLMs (ChatGPT-4, Gemini-2.0, Claude-3.7, Grok-3, DeepSeek-R1, Qwen-2.5). Each model was tested in Turkish and in English, under both batch and single-item prompt formats. The strengths and weaknesses of the models were tested under different conditions.

Results: Claude-3.7 and Grok-3 performed best (~83-84% correct) with low variance, whereas Qwen-2.5 and DeepSeek-R1 had lower accuracy (~75%) with more simple errors. Across all models, switching from Turkish to English increased median accuracy by 19.5% ($P = 0.028$). In contrast, batch vs. single-item prompting showed no overall performance difference ($P = 0.280$). DeepSeek-R1 was markedly slower (≥ 10 minutes per question vs ~134 seconds for others, $P < 0.001$). All models achieved high accuracy on common conditions but struggled with nuanced cases and negatively phrased questions.

Conclusion: Current LLMs can answer standard dermatology certification questions with moderate to high accuracy, especially in English. However, they are still susceptible to linguistic traps, negation, and nuanced clinical distinctions. Before they can be routinely used for educational or clinical purposes, optimization for Turkish language input and complex reasoning is necessary.

Keywords: Large language models (LLMs), artificial intelligence in dermatology, Turkish dermatology board examination, multilingual ai performance, prompt engineering

Introduction

Artificial intelligence (AI) technologies are used as an effective tool in medical education to support the acquisition of theoretical knowledge and improve the clinical skills of medical students and residents.[1] The increasing use of AI applications in medical education has potential, especially in disciplines based on visual diagnoses, such as dermatology; this trend necessitates re-evaluating conventional assessment tools, such as specialty competency exams, with AI models.[2] Studies on the performance of AI models in medical education exams reveal the potential, limitations, and room for improvement of this technology.[3] Recent benchmark studies show that state-of-the-art large language models (LLMs) (e.g., GPT-4, Gemini Advanced, Claude) can exceed the 60% pass mark on united states medical licensing examination step 1-style items and perform at or near the resident level in ophthalmology and orthopedic vignette sets.[3-5]

Despite the progress made, two critical knowledge gaps remain. First, almost all validation studies have been conducted in English, while more than half of the world's medical

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students study in other languages. LLMs show significant performance declines in low-resource languages due to issues such as imbalanced training data, cultural differences, and tokenization problems.[6-8] Second, there has been limited research into domain-specific, high-stakes examinations that assess nuanced clinical reasoning rather than just general medical knowledge.

The Turkish Dermatology Society (TDS) qualifying examination combines essential knowledge with image-rich clinical scenarios and is primarily administered in Turkish. To our knowledge, no published study has yet assessed contemporary LLMs using this examination, nor has any compared their performance when identical items are presented in Turkish versus professionally translated English. Addressing this gap is crucial for two main reasons. First, educators need evidence before incorporating AI into residency training. Second, algorithm developers require detailed error profiles to optimize multilingual models and prevent hallucinations or unsafe recommendations.

In this study, we conducted a comparative performance analysis of six publicly accessible LLMs using multiple-choice questions from the TDS qualifying examination. To explore the effects of linguistic and structural variations on model performance, we tested each model under four prompting conditions that varied by input language (Turkish vs. English) and delivery format (batch vs. single-item). By systematically comparing accuracy, response latency, and error characteristics, we aimed to evaluate the dermatological knowledge base as well as the language adaptability of these models. We, therefore, benchmarked six contemporary LLMs on 200 standardized text-only TDS board items to quantify language-related and prompt-related performance shifts and to characterize error profiles relevant to clinical reasoning.

Materials and Methods

Study Design

In this study, a prospective benchmarking comparing the performance of six publicly available LLMs on the dermatology specialty examination was conducted (Table 1). All analyses were performed between 15 February and 1 March 2025 to minimize version drift. Each model was initialized in a fresh "clean" account session to avoid any carryover of prior context. No plug-ins or speech memory features were activated.

Question Bank

Two hundred multiple-choice questions were selected from the publicly available repository of the TDS qualifying examination. Items based on clinical photographs or histopathology images were excluded to keep the assessment entirely text-based, and questions assessing epidemiology, pathophysiology, clinical diagnosis, and treatment were included.

Translation

The initial English drafts of all 200 Turkish board examination items were created using DeepL Pro (v3.5). Subsequently, a senior dermatology resident proficient in academic English (N.Ç.) and a professional dermatologist with a high level of proficiency in academic and clinical English (A.U.A.) reviewed the machine translations. Together, they reached a consensus, correcting any inaccuracies in medical terminology and addressing cultural nuances.

Prompting Conditions

Batch conditions involved multiple questions uploaded simultaneously, whereas single-item conditions involved uploading questions individually. During batch uploading, four separate Word files were uploaded one by one (batch Turkish 2015, batch Turkish 2017, batch English 2015, batch English 2017). In single-item (sequential) prompting, 400 questions were uploaded individually each time.

Outcome Measures

For each method, the response times and accuracy rates of the models were analyzed. The language factor was examined by averaging the batch and single-item prompting results. The official answer key was used as a reference. For each correct answer, 1 point was given and 0 points for an incorrect answer; the total number of correct answers and the success percentage of each model were calculated. Correct answer rates were reported separately for each model and method, and comparisons were made between models and methods. In addition, questions that all models answered incorrectly, questions that only one model answered correctly (superior performance), and questions that only one model answered incorrectly (simple error) were analyzed. Across all four methods, any question answered incorrectly by at least five of the six models was defined as a "difficult question". Also, all 200 questions were categorized into six content domains: (1) common dermatoses and first-line management, (2) clinical case vignettes, (3) rare syndromes and eponyms, (4) disease sub-typing, (5) negatively worded stems, and (6) other. Accuracy was subsequently assessed for each category to enable a category-based performance analysis. In the batch Turkish method, the response times of the models were determined using a stopwatch.

TABLE 1. Details of the language models used in this study, including provider platforms and access dates

Model	Provider (API/UI)	Date Accessed
ChatGPT-4.0	OpenAI (web)	18 Feb 2025
Gemini 2.0 Flash	Google DeepMind (web)	21 Feb 2025
Claude 3.7 Sonnet	Anthropic (web)	17 Feb 2025
Grok-3	xAI (web)	20 Feb 2025
DeepSeek R1	DeepSeek AI (web)	19 Feb 2025
Qwen 2.5	Alibaba (web)	20 Feb 2025

AI: Artificial intelligence, API: Application programming interface, UI: User interface

Statistical Analysis

All statistical analysis were performed using IBM SPSS Statistics v26.0 (IBM Corp., Armonk, NY) software. The distribution of continuous variables was examined using the Shapiro-Wilk test, and non-parametric tests were preferred when the normality assumption was not met. The significance level was set at $P < 0.05$ for all tests.

Language effect: The average performance of the models in Turkish (batch Turkish + single-loading Turkish) and English (batch English + single-loading English) formats was compared using the paired Wilcoxon signed-rank test.

Method effect: The effect of the batch and single-loading methods in each language group was analyzed using the paired Wilcoxon test.

Response time analysis: The average response time of the DeepSeek model was compared with the response times of other models using the Mann-Whitney U test due to the non-normal distribution of the data. The Kruskal-Wallis test was used to compare models other than DeepSeek.

Difficult questions and word count: The average number of words in difficult questions that were answered incorrectly by all models or correctly by only one model, was analyzed using the Mann-Whitney U test.

Ethical Considerations

The study analyzed publicly available examination material and generated AI responses; it involved no human participants or patient data and therefore did not require Institutional Review Board approval. All procedures conformed to the Declaration of Helsinki principles for non-interventional research.

Data Availability

Full prompt templates, anonymized model outputs, and analysis scripts can be requested from the corresponding author if needed.

Results

Overall Performance Evaluation by Model

When analyzing the overall number of correct answers and average performance of the models using the "batch Turkish" and "single-loading Turkish" methods, the Claude (84.0%±0.00) and Grok-3 (83.0%±3.83) models demonstrated the most successful results, showing the highest average number of correct answers and low standard deviations. In contrast, the Qwen 2.5 (74.25±613) and DeepSeek (75.5%±7.05) models displayed the lowest performance and highest inconsistency, indicated by both lower average correct answer counts, and particularly, for DeepSeek, higher standard deviation values (Figure 1).

However, some models demonstrated superior performance in specific domains. For example, among the 200 questions, there were items that only Qwen 2.5 answered correctly while all other models failed, suggesting areas where it outperformed its peers.

Impact of Language Factor

There was a significant performance advantage for English versus Turkish prompts across models ($P = 0.028$). This result indicates that LLMs perform significantly better in English than in Turkish. A noticeable performance improvement was observed across all models when switching to English questions (Figure 2). In particular, the ChatGPT and Qwen 2.5 models were the most positively impacted by the language change.

Effect of Method Factor

The DeepSeek model demonstrated a significant performance improvement in the Turkish single-item prompting method compared to the Turkish batch method, showing the largest gain from this approach. In contrast, the single-loading method led to a performance decline in the ChatGPT and

Gemini models. When comparing batch and single-loading methods, no statistically significant difference was observed between the methods ($P > 0.05$). However, per-model analyses revealed notable individual differences beyond this general finding (Figure 3).

Simple Errors and Inconsistencies

In the analysis of "simple errors," the DeepSeek and Qwen 2.5 models had the highest number of simple errors. DeepSeek recorded the most errors with a total of 27, followed by Qwen with 22 (Figure 4a). When comparing prompting conditions, the Turkish batch condition yielded the most errors, whereas the English single-item condition had the fewest (Figure 4b).

Word Count Analysis of Difficult Questions

The difficult questions had a significantly lower average word count than other questions (9.71±7.08 vs. 11.9±9.89 words; $P = 0.019$), suggesting that shorter questions tended to pose more of a challenge (Figure 5).

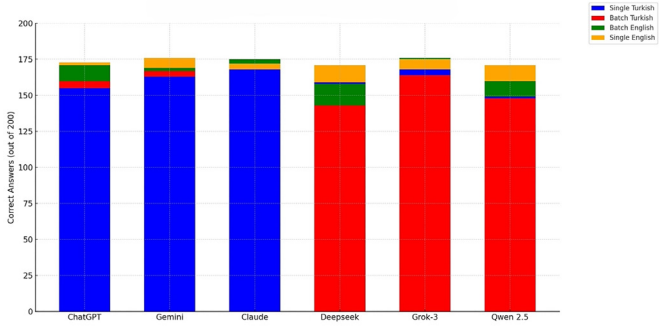

Figure 1. Prompting condition. Stacked segments represent the number of questions each model answered correctly in four prompting conditions: single-item Turkish (blue), batch Turkish (red), batch English (green) and single-item English (orange)

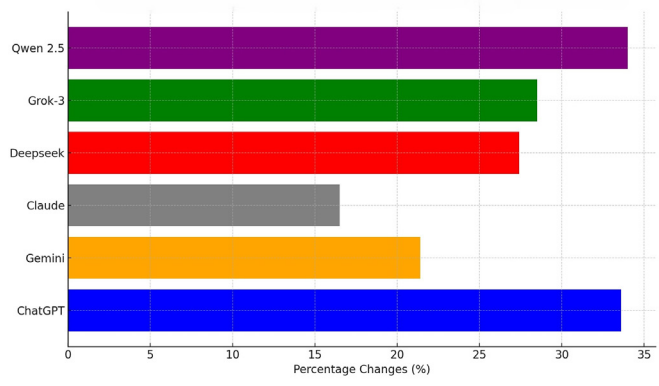

Figure 2. English versus Turkish condition. Horizontal bars show the absolute percentage-point reduction in model error rates when item prompts are translated into English. A positive value indicates higher accuracy in English

Category-Based Performance Evaluation

When evaluating the full set of results across 200 questions, six language models and four prompting methods, the models achieved over 90% accuracy in most categories, including common disease presentations, primary diagnoses, and

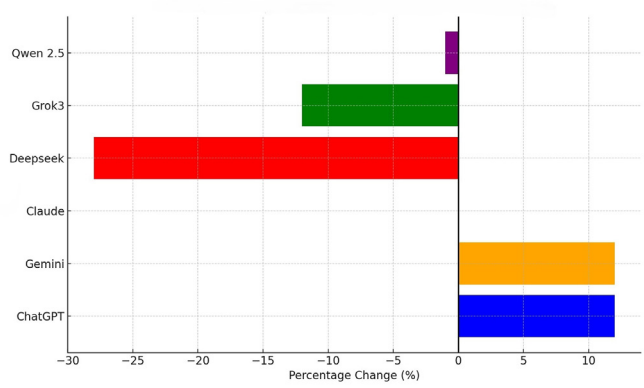

Figure 3. Batch versus single-loading condition. Bars show the percentage-point difference in error rates when models were prompted in batch versus single-item format. Negative values indicate that the model made fewer errors when given one item at a time

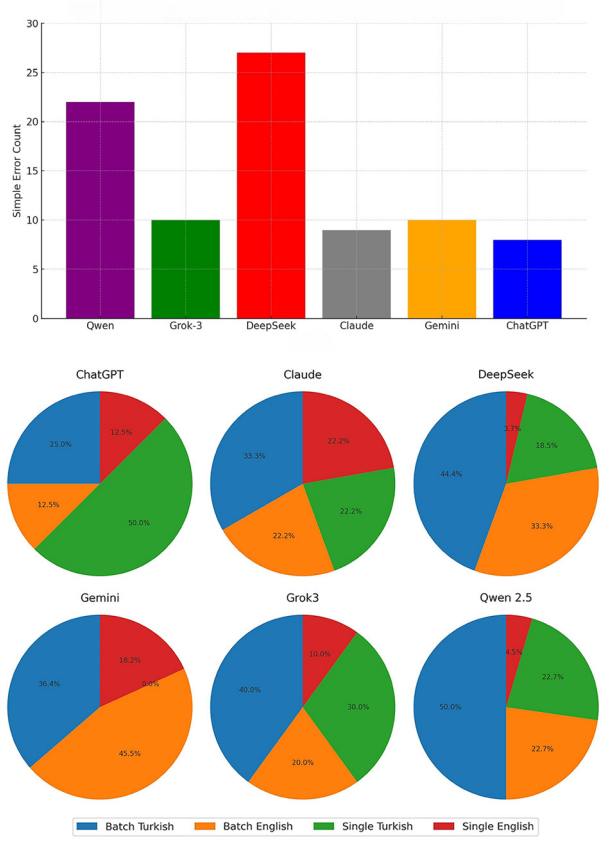

Figure 4. Simple error distribution by model and prompting condition. (a) Total number of simple errors made by each model across all tasks (b) Proportional distribution of simple errors per model under four prompting conditions: single-item Turkish, batch Turkish, batch English, and single-item English

treatment approaches, clinical case scenarios, and questions involving specific medical terminology or rare syndromes. In contrast, the lowest accuracy rates were observed in distinguishing clinical subtypes (57.14%) and in handling negatively phrased questions (83.33%) (Table 2).

Response Time: Performance or Speed?

DeepSeek demonstrated a significantly longer response time, consistently exceeding 10 minutes per item (720 seconds), while the other five models responded within a comparable time frame (mean: 134±73.85 seconds), with no statistically significant differences observed among them ($P > 0.05$) (Table 3).

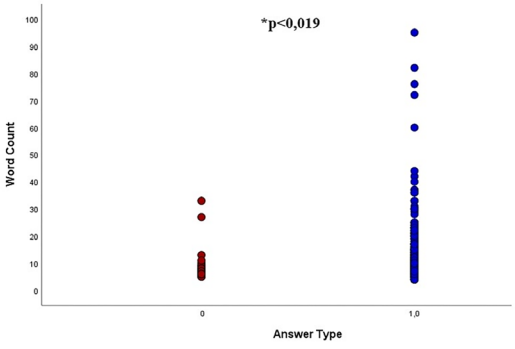

Figure 5. Word count and accuracy relation. Each point represents a board question, plotted by word count and whether it was answered correctly (1) or not (0). Incorrectly answered questions had significantly shorter text length ($P < 0.019$)

Discussion

This study presents the first direct comparison of six contemporary LLMs using the TDS qualifying examination. Three key findings stand out. First, the language used was the primary factor influencing performance: switching from Turkish to English improved the median accuracy significantly, benefiting all tested LLMs. Second, the presentation method had minimal overall impact; however, DeepSeek R1 performed significantly better with single-item prompts. Third, even the best-performing models faced challenges with nuanced clinical differentiation, negatively worded questions, and time efficiency. This highlights ongoing limitations in contextual reasoning and practical usability.

The results of the overall performance evaluation showed that LLMs have gained significant competence in interpreting and applying medical knowledge. The consistent performance of the Claude and Grok-3 models, suggests that these models have a more balanced information processing capacity. Claude has shown successful performance in studies evaluating LLMs.[9] In radiology board exams, Claude outperformed Bard and Gemini Pro by achieving 62% accuracy.[9] In NBME exams, it again performed similarly to GPT-3.5 and Bard with a score of 84.7%.[10] Grok 3, on the other hand, is still under development, and while it shows potential in interaction skills and mathematical reasoning, its performance in medical exams has not yet been extensively evaluated.[11] As both models continue to evolve, their role in medical education and examinations will likely expand, and they will need to be

TABLE 2. Accuracy of language models across predefined dermatology question categories (category-based analysis)

Category	Items (n)	Accuracy (%) ± SD
Common dermatoses / first-line management	35	97.1 ± 16.5
Clinical case vignettes	27	94.4 ± 8.0
Rare syndromes / eponyms	22	95.5 ± 10.0
Disease sub-typing	21	57.1 ± 1.0
Negatively worded stems	12	83.3 ± 20.0

SD: Standard deviation

TABLE 3. Response times and performance characteristics of each language model

Model	Response Time	Description
ChatGPT 4.0 (OpenAI)	80 seconds	Fast and stable
Gemini 2.0 Flash (Google DeepMind)	50 seconds	The fastest responding model
DeepSeek R1 (DeepSeek AI)	>10 minutes	Extremely slow / server congestion
Grok 3 (xAI)	180 seconds	Moderate waiting time
Claude 3.7 Sonnet (Anthropic)	230 seconds	Slow responding model
Qwen 2.5 (Alibaba)	120 seconds	Balanced response time / Medium speed

AI: Artificial intelligence

regularly re-evaluated and refined to ensure their reliability and relevance in the field.[11] On the other hand, Qwen 2.5 and DeepSeek's fluctuating performance and susceptibility to simple errors reflect differences in model architectures and training strategies.[12,13]

It was observed that the language factor had a significant effect on the AI models. The significantly higher performance of the models on English questions compared to Turkish questions reveals the dominance of English data sets in the training processes of LLMs.[14,15] This aligns with reports in the literature that LLMs perform worse in languages other than English.[6,7] LLMs are more successful in English in part because of the vast amount of English digital content and the concentration of AI research on English, owing to that language's global dominance.[15-17] Non-English languages present unique challenges (e.g., cultural nuances, complex linguistics) that require specialized AI approaches. A lack of standardized resources and tools in these languages, can lead to issues like cultural hallucinations, making it more difficult to develop effective AI models for them.[8] Despite English's privileged position in AI development, there is growing recognition of the need to improve LLM performance in other languages. Initiatives like cross-language training and multilingual model development are working to create more inclusive, culturally sensitive AI systems.[14,18]

Although there was no statistically significant difference between batch and single-item prompting in the analyses regarding the method factor, model-based differences are noteworthy. The performance improvement of the DeepSeek model in the Turkish single-item prompting method suggests that some models are more sensitive to sequential processing.[19] AI systems designed for sequential processing use character recognition, on-the-fly verification, and error correction mechanisms to ensure accuracy during real-time data entry.[19,20] These approaches provide high accuracy and user efficiency by reducing errors in data entry.[19] This finding suggests that the prompt dependency and context management capabilities of LLMs may vary from model to model.[21] Unlike DeepSeek, models like ChatGPT and Claude experienced a decline in performance under the same conditions, underscoring the importance of tailoring LLM deployment strategies to model-specific strengths and intended use cases.

In particular, category-based analyses clearly revealed the strengths and weaknesses of AI models. High success rates in basic medical knowledge and common conditions confirm the potential of these models to provide knowledge-based support in general medical practice.[22] However, high error rates in distinguishing clinical subtypes of diseases and negatively worded question stems suggest that AI models still have limitations in analyzing context in depth and overcoming linguistic pitfalls.[23-25]

This finding is in line with the known difficulties of negation and contextual disambiguation in natural language processing systems.[26,27] Moreover, the questions that stumped all models were notably short, suggesting that LLMs make more errors on context-free, brief, and ambiguous statements. As previous studies also suggest, LLMs are heavily context-driven, and their performance degrades when information is lacking.[28]

In terms of response times, the trade-off between speed and another aspect of performance must also be considered. For AI systems used especially in clinical applications, not only accuracy but also speed in practical use is critical.[29]

From an educational perspective, LLMs already demonstrate near-expert-level performance on routine factual dermatology content and could be useful as supplementary tutoring tools, particularly when prompts are provided in English. However, their susceptibility to short, context-poor questions and semantic traps presents a risk if they are used uncritically for high-stakes self-assessment. Moreover, DeepSeek R1's extremely long response time (over 10 minutes per question) makes real-time feedback impractical.

Study Limitations

Several limitations should be taken into account when interpreting our findings. First, our analysis was limited to 200 publicly available, text-only multiple-choice items. This excluded image-based and open-ended questions, which are essential in dermatology practice, therefore, the model's performance on multimodal or free-text tasks remains unassessed. Second, due to the rapid development of LLMs architectures and public interfaces, our results reflect the model versions as of February 2025 and may not apply to future iterations. Third, all assessment items were derived from a single national board examination, which restricts the external validity to other dermatology curricula or broader medical fields. Lastly, we used a binary scoring approach, giving credit only for fully correct responses. This approach may underestimate partial reasoning or nuanced understanding that could be better evaluated using a rubric-based scoring system. Addressing these limitations will require larger, multimodal test sets, ongoing reassessment of evolving model versions, and the integration of more detailed qualitative scoring frameworks.

Conclusion

In conclusion, this study demonstrated the potential and current limitations of AI models in medical education and assessment processes from a multidimensional perspective Our findings indicate that, while AI systems can be valuable tools for medical decision support, they still require improvement in

areas such as linguistic diversity, contextual analysis, and use-case optimization. Future research should focus on developing multilingual and culturally sensitive models, enhancing context management capabilities, and optimizing the speed-accuracy balance, particularly in clinical applications.

Ethics

Ethics Committee Approval: Not applicable.

Informed Consent: Not applicable.

Footnotes

Authorship Contributions

Concept: A.U.A., Design: A.U.A., N.Ç, Data Collection or Processing: A.U.A., N.Ç, Analysis or Interpretation: A.U.A., N.Ç, Literature Search: A.U.A., N.Ç, Writing: A.U.A., N.Ç.

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Original Article

Dermoscopy-Guided Surveillance in Xeroderma Pigmentosum: A Retrospective Analysis

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Abstract

Aim: Xeroderma pigmentosum (XP) is a life-threatening disease characterized by high rates of skin cancers. Therefore, it is important to establish key guidelines for the follow-up of these patients to detect skin cancers, particularly melanoma, at an early stage.

Materials and Methods: This is a retrospective study that includes the analysis of the follow-up findings and medical records of XP patients who were followed up with whole-body skin examination, dermoscopic examination, and whole-body photographing between 2003 and 2021 in the Dermato-Oncology unit of Ege University Department of Dermatology.

Results: Of the 19 patients, 10 were male and 9 were female. The youngest patient was 5 years old, while the oldest patient was 64 years old. A total of 234 lesions were excised from these patients. Seventeen melanomas were excised, including 11 *in situ*, with a Breslow thickness of less than 1 mm. The highest Breslow scores belong to patients who missed their appointments or did not receive follow-up care previously.

Conclusion: It was observed that regular full-body skin examinations, whole-body photography, and dermoscopic monitoring performed at 3-month intervals in XP patients are helpful in detecting skin malignancies at an early stage and preventing unnecessary excisions.

Keywords: Xeroderma pigmentosum, dermoscopy, basal cell carcinoma, squamous cell carcinoma, melanoma

Introduction

Xeroderma pigmentosum (XP) is an autosomal recessive genetic disease that affects the DNA repair system necessary to repair DNA damage caused by ultraviolet radiation.[1] It is characterized by marked photosensitivity, facial freckles that appear before the age of 2, ocular findings including keratitis and photophobia, and an early onset of skin malignancies such as basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma.[2] In XP patients under 20 years of age, the risk of developing non-melanoma skin cancer is 10,000 times higher, while the risk of developing melanoma is 2,000 times greater compared to the general population.[3] Due to the high rates of skin cancers, this disease can be life-threatening, and the prognosis depends on the patient's awareness of the disease, sun protection measures and early diagnosis of skin cancers.[4] However, widespread actinic damage characterized by multiple lentigines, actinic keratoses, and poikiloderma complicates the diagnosis of skin tumors in these patients. In this context, dermoscopy serves as a non-invasive tool that aids in the early diagnosis of skin tumors in these individuals.[5] Few reports in the literature discuss the role of dermoscopic follow-up in the early detection of skin tumors in XP patients.[5,6] In our study, we aimed to highlight the importance of dermoscopic follow-up for the early detection of skin tumors in XP patients.

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Materials and Methods

Our study ethical approval was obtained from the Ege University Medical Research Ethics Committee (approval number: 21-11.1T/46, date: 18.11.2021). Consent was obtained to analyze patients' medical records for the study. Patients with XP underwent whole-body skin examinations, dermoscopic examinations, and whole-body photographs between 2003 and 2021 at the Dermato-Oncology unit of Ege University Department of Dermatology. Patients were followed up every three months with total body photographing whole body dermoscopic examination. In the present study, we analyzed the follow-up findings and medical records of these patients. We noted their age, sex, follow-up duration, and the pathology reports of excised skin tumors, and melanocytic lesions.

Statistical Analysis

All data were analyzed descriptively. Continuous variables were summarized as mean ± standard deviation, and categorical variables were presented as frequencies and percentages. No comparative statistical tests were performed due to the descriptive and retrospective design of the study.

Results

Patients' Demographics Features

A total of 19 XP patients were followed up between 2003 and 2021 in the Dermato-Oncology Unit of the Department of Dermatology at Ege University. Fourteen of these patients attended follow-up visits regularly, while five patients did not attend consistently for unknown reasons. Of the 19 patients, 10 were male and nine were female. The youngest patient was 5 years old, and the oldest patient was 64 years old. The mean age was 24.97 (±15.07), with the mean age for male patients being 22.7 (±12.29) and for female patients being 27.4 (±17.31). A total of 234 lesions were excised from these patients.

Skin Cancer Development Age

The earliest age of BCC development was 7, the SCC development age was 6, and melanoma development was 8. The mean ages of BCC, SCC, and melanoma were 20.15 [±13.56, minimum (min.): 7, maximum (max.): 59], 23.22 (±12.42, min.: 6, max.: 47), and 18.3 (±7.9, min.: 8, max.: 28), respectively.

Skin Cancer Characteristics

Basal Cell Carcinoma

In total, 139 BCCs were excised. The histopathological types of these BCCs included 38 nodular, 12 superficial, 9 micronodular, 8 infiltrative, 6 noduloulcerative, 6 ulceroinfiltrative, 3 ulcerative, 2 morpheaform, 7 mixed type, and 1 bowenoid type. The type was not specified in the pathology report for 47 cases. The highest number of BCCs in a single patient was found to be 56, followed by 42. Additionally: a 64-year-old female patient who had been followed up for 10 years and had a single instance of BCC was remarkable due to her generally stable health status.

Squamous Cell Carcinoma

A total of 44 SCCs were excised, 6 of which were located in the lip mucosa and the others were cutaneous. Fifteen of these SCCs were *in situ*, 9 were well-differentiated, 5 were moderately differentiated, 8 were poorly differentiated, 4 were microinvasive, 1 was keratoacanthoma-like type, and the type of 2 was unspecified in the pathology report. In addition, five conjunctival SCCs, three corneal SCCs *in situ*, and one high-grade squamous intraepithelial neoplasia in the cornea were excised by ophthalmologists.

Melanoma

Only 5 of 19 XP patients developed melanoma during the follow-up. A total of 17 melanomas were excised, five of which were excised from a single patient. Among these, 11 melanomas were *in situ*, 5 of which were lentigo maligna. The Breslow thicknesses of the other patients were as follows, in order from the lowest to the highest: 0.27 mm, 0.9 mm, 0.93 mm, 2.3 mm, 5.6 mm, and 15 mm. One patient was referred to our unit for the first time with melanoma metastasis in a lymph node of unknown origin; prior to this, he had never been followed by dermoscopy.

Other Malignant and Benign Tumors

Other excised malignant tumors included 5 atypical melanocytic proliferations, 1 atypical fibroxanthoma, 1 melanocytic tumor with regressive changes, 1 melanocytic tumor of uncertain malignant potential, 3 angiosarcomas, and 1 vascular tumor with uncertain malignant potential. A total of 22 benign lesions were excised, including 6 compound nevi, 6 junctional nevi, 3 dysplastic nevi, 2 lentiginous nevi, 2 dermal nevi, 1 dermal melanocytic hamartoma, 1 lentiginous hyperplasia, and 1 spitz nevus.

Discussion

The literature on the role of dermoscopic follow-up in XP patients is limited. To the best of our knowledge, there are only two reports regarding dermoscopic follow-up in XP patients. Firstly, Malvehy et al.[5] reported dermoscopic findings of melanoma and non-melanoma skin cancers in two siblings who were followed for nearly 5 years. They suggested that distinguishing between benign and malignant tumors based solely on clinical examination is difficult, but dermoscopy aids in deciding on excision and helps detect melanoma at an early stage.

Green et al.[6] demonstrated that an XP patient followed for 23 years developed 38 primary melanomas, SCCs, and 70 BCCs during follow-up. They also stated that none of the melanomas in this patient exhibited deep local invasion or metastasis. The authors monitored this patient with a whole-body skin examination, whole-body photographs, and dermoscopic assessments at 6-week intervals. They noted that many new melanomas were detected within 6 weeks. Thus, the authors recommended combining whole-body skin examination, photography, and dermoscopy at short intervals in the management of XP patients.

In the present study, most cases were detected at the *in situ* stage in both SCCs and melanomas (Figure 1). Additionally, many melanomas were identified while still at a thin Breslow thickness. The patient with the highest Breslow thickness had not been previously followed up and was referred to the Dermato-Oncology unit by plastic surgery. This finding supports the crucial role of regular patient follow-up through total body examinations, total body photography, dermoscopic monitoring, and dermoscopic photography of suspicious skin lesions for the early detection of melanomas. Although the diagnostic accuracy of dermoscopy was not evaluated quantitatively in this retrospective study, all excised melanomas exhibited dermoscopic features suggestive of malignancy, such as asymmetric pigmentation, atypical network, and irregular streaks. Dermoscopy was instrumental in selecting lesions for excision.

Green et al.[6] recommended follow-up at 6-week intervals. However, our study results indicate that follow-up performed at 3-month intervals is also sufficient to detect melanoma in their early stage. Additionally, follow-up intervals can be adjusted based on the frequency of skin cancer and suspicious skin lesions in the patient, provided the patient adequately complies with sun protection measures. It was noted that the patient with melanoma, having a Breslow thickness of 5.6 mm, did not seek examination for a long time, and consequently, the lesion reached this stage. Additionally, it was noted that this same patient had the highest number of melanomas and BCCs in our series; and they frequently delayed appointment dates and did not comply with sun protection recommendations. This serves as a unique example of how the patient's adherence to regular follow-up and sun protection influences early melanoma diagnosis.

The total number of benign lesions excised from the patients was 22, with some being congenital, others removed due to atypical criteria, and changes during follow-up, and some excised alongside the malignant tumor as they were located near it (Figure 2). It was observed that a total of 76 benign lesions were excised at the external center before the patient, who began to be followed up at the age of 27, was admitted.

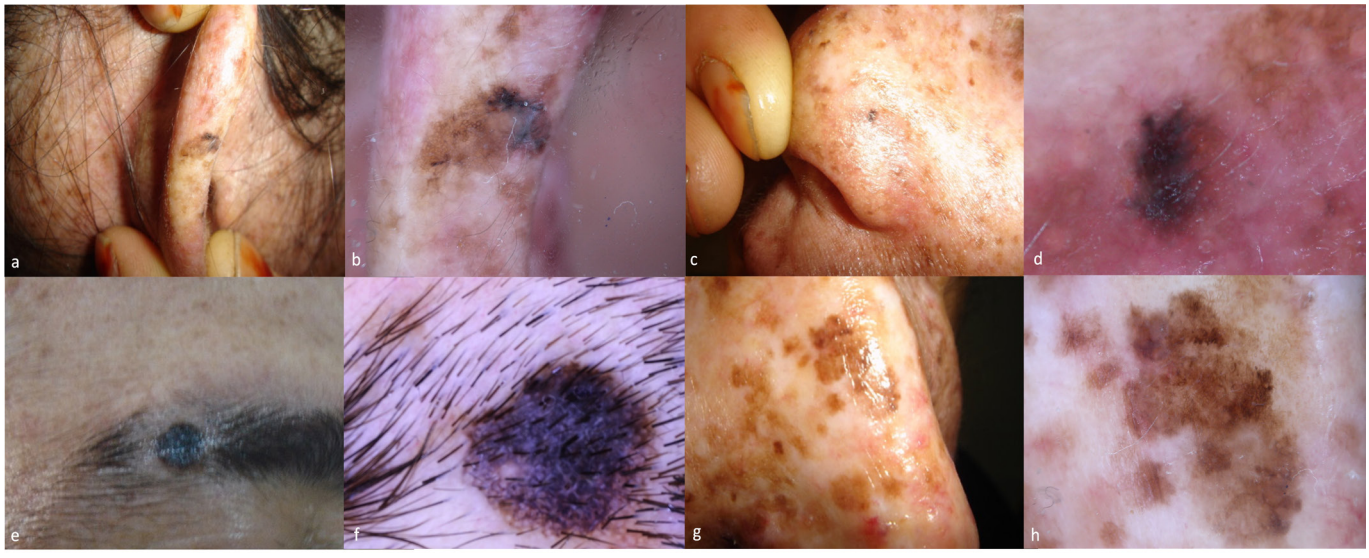

Figure 1. Clinical and dermoscopic pictures of (a, b) an *in situ* melanoma on the ear helix, (c, d) a tiny lentigo maligna on the patient's nose, (e, f) a sneaky melanoma (stage T1B) hiding behind thick eyebrows, and (g, h) lentigo maligna on the patient's nose

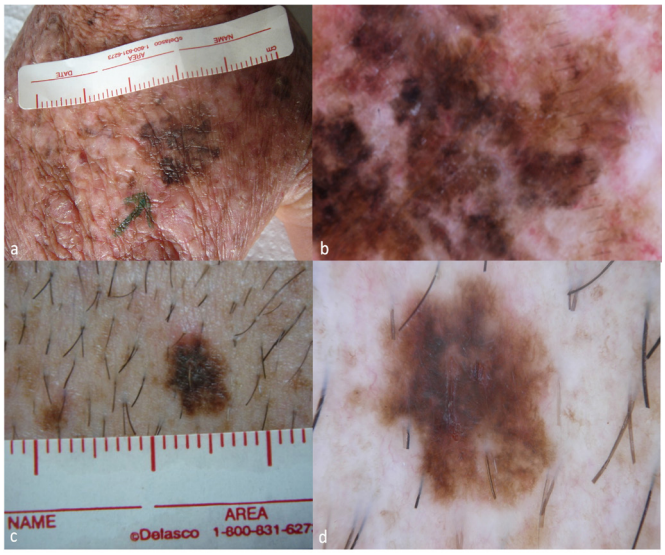

Figure 2. (a, b) Clinical and dermoscopic images of lentiginous hyperplasia mimicking melanoma; (c, d) An "ugly duck" lesion was found to be a dysplastic nevus on histopathology

These excision numbers for a single patient are significantly higher than our total number of melanocytic lesion excisions across all patients under follow-up, and highlight the importance of dermoscopic follow-up in reducing excision rates among these patients. Preventing unnecessary excisions is important in reducing the cost and undesirable cosmetic outcomes associated with redundant surgical procedures. Therefore, decline in the quality of life for patients is prevented.

Study Limitations

One important limitation of this study is the lack of genetic subtyping of XP patients. Due to the retrospective design and the long duration of follow-up (starting in 2003), routine genetic testing was not performed in most cases. As a result, genotype-phenotype correlations could not be assessed. Future prospective studies incorporating genetic data may help clarify subtype-specific cancer risks in XP.

Conclusion

Our patient series shows that regular full-body skin examinations, whole-body photographs, and dermoscopic monitoring performed at three-month intervals in XP patients are crucial for detecting skin malignancies at an early stage and preventing unnecessary excisions in these patients.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ege University Medical Research Ethics Committee (approval number: 21-11.1T/46, date: 18.11.2021).

Informed Consent: Consent was obtained to analyze patients' medical records for the study.

Footnotes

Authorship Contributions

Concept: G.O., N.D., B.Y., T.A., I.K., Design: G.O., N.D., B.Y., T.A., I.K., Data Collection or Processing: G.O., N.D., B.Y., T.A., I.K., Analysis or Interpretation: G.O., N.D., I.K., Literature Search: G.O., N.D., I.K., Writing: G.O., N.D., I.K.

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Original Article

Monocyte-To-Lymphocyte Ratio May Be a Clue to Understand Underlying Cause of Pruritus in Chronic Kidney Disease

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Abstract

Aim: Pruritus is one of the most common dermatologic conditions in chronic kidney disease (CKD) patients. Uremic toxins, inflammation, imbalance in mineral metabolism, and altered hormonal status may constitute underlying causes. The present study aims to evaluate the association between inflammatory markers and pruritus, with or without the presence of xerosis, in CKD.

Materials and Methods: This observational and cross-sectional study compared CKD patients with pruritus and xerosis with CKD patients without pruritus and xerosis regarding inflammatory markers. Peripheral blood-derived inflammatory markers such as neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio were analyzed.

Results: A total of 92 patients were included in the study, 47 (51.1%) of whom had xerosis and/or pruritus. Pruritus and xerosis were significantly associated ($P < 0.001$), but there were also CKD patients with pruritus and without xerosis (28%). MLR was significantly higher in patients with pruritus, and in patients with both xerosis and pruritus, than in those without ($P = 0.037$ and $P = 0.046$, respectively). Dialysis status was not associated with pruritus ($P = 0.911$), and CRP levels in patients with dialysis were higher than those who did not receive dialysis ($P = 0.046$).

Conclusion: Higher MLR in patients with CKD-associated pruritus may suggest a role for monocytes in the mechanism of pruritus, where low-grade inflammation of CKD is an underlying cause. In the future, therapeutic measures to reduce monocyte activity may be studied to treat CKD-associated pruritus.

Keywords: Chronic kidney disease, inflammation, monocyte-to-lymphocyte ratio, pruritus

Introduction

Kidneys play a vital role in maintaining several critical physiological processes in the body, with both exocrine and endocrine functions. Exocrine functions include regulating fluid and electrolyte balance, acid-base equilibrium, and the removal of metabolic waste products, while endocrine functions involve activating vitamin D for calcium balance, blood pressure regulation, and erythropoiesis through hormone production.[1]

Chronic kidney disease (CKD) affects approximately 861 million people worldwide, with the majority suffering from the disease in its progressive form.[2] CKD is characterized by the gradual, irreversible loss of kidney function, leading to the accumulation of waste and fluids in the body. This condition arises from factors such as diabetes, hypertension, infections, autoimmune diseases, and genetic disorders, with diabetes and hypertension being the most common causes.[3]

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In addition to systemic effects such as appetite and weight loss, fatigue, headache, hematuria, edema due to fluid retention, and electrolyte imbalances, CKD can present with a range of dermatological changes, often due to fluid and electrolyte imbalance, impaired hormone production, and the accumulation of waste products in the blood.[4] These changes include leukonychia, melanonychia, half-nail signs, xerosis, hyperpigmentation, pallor, pruritus, infectious diseases, skin thinning, and ecchymosis.[5]

Xerosis and pruritus are common dermatological symptoms in CKD patients, and while the exact mechanisms are not fully understood, several factors contribute to their development. Imbalances in electrolytes, especially calcium and phosphate, lead to the accumulation of these substances in the skin and blood vessels. Additionally, impaired kidney hormone production can affect skin glands, leading to dryness and increased infection risk.[5] Although previous theories pointed to histamine release as the cause of pruritus in CKD, current views suggest a non-histaminergic pathway as the underlying mechanism.[6,7]

Chronic pruritus is an unpleasant sensation associated with wanting to scratch, lasts more than 6 weeks, and is a common and potentially debilitating symptom in CKD patients.[7] It is often associated with anxiety, depression, and sleep disturbances, and severe pruritus has been identified as an independent risk factor for increased mortality and poor prognosis.[8] The pattern of pruritus in CKD tends to be widespread, intermittent, and symmetric, often affecting the legs, back, and scalp, with a tendency to worsen at night. Unlike other causes, CKD-related pruritus has no primary skin lesion but may lead to secondary excoriations due to chronic scratching.[7]

Inflammatory markers are known to correlate with CKD, and their presence contributes to kidney damage and the development of associated symptoms. Elevated inflammatory markers in CKD are also linked to fatigue, reduced appetite, and increased risks of both mental and physical dysfunction. Given the significant relationship between CKD and inflammation, it is crucial to explore how inflammatory markers might impact dermatological changes in CKD patients.[9]

This study aims to evaluate the impact of inflammation on xerosis and pruritus in CKD patients and investigate the connection between these markers and dermatological findings. The results may help develop new approaches to optimizing renal and dermatological management strategies in CKD patients.

Materials and Methods

This cross-sectional and observational study received approval from the Non-Interventional Clinical Research Ethics Committee of Uşak University Faculty of Medicine (approval number: 386-386-08, date: 06.06.2024).

Patients aged 18 years or older with a confirmed diagnosis of CKD, and giving informed consent to participate, were included in the study. CKD diagnosis is based on the "2024 Kidney Disease: Improving Global Outcomes" guidelines.[10] Patients with other inflammatory dermatological conditions causing xerosis and pruritus, active infections, inflammatory diseases, or those using medications or having conditions likely to elevate inflammatory markers were excluded from the study.

Age, sex, dialysis status, and physical examination findings such as xerosis and pruritus of the patients were demographic and clinical variables that were analyzed. The severity of xerosis was assessed using a clinical grading scale proposed by Weber et al.[11] This scale evaluates two main parameters: visible dryness and tactile roughness, each scored from 0 (absent) to 4 (extreme). A higher score indicates greater severity of xerosis, integrating visual and tactile clinical observations.

- **Score 0 (absent):** No visible dryness; skin is perfectly smooth and pliable.
- **Score 1 (slight):** Slight scaling and dull appearance with slightly irregular and rough tactile evaluation.
- **Score 2 (moderate):** Presence of minor scales, whitish appearance, and definite roughness; tactile evaluation shows irregularity and slight stiffness.
- **Score 3 (severe):** Uniformly distributed small and larger scales, redness, and some superficial cracks; advanced irregularity and rough feeling with associated stiffness.
- **Score 4 (extreme):** Dominated by large scales, redness, cracks, and eczematous changes; gross irregularity and severe disturbance of skin markings with definite stiffening.

Pruritus severity was evaluated with a 10-point Visual Analog Scale (VAS), where 0 represents no pruritus, and 10 indicates the worst imaginable pruritus.

Blood samples were analyzed for C-reactive protein (CRP) and complete blood count with differentials. Systemic inflammatory indices were calculated:

- **Systemic Inflammation Index (SII):** Neutrophil × Platelet/Lymphocyte.
- **Systemic inflammatory response index (SIRI):** Neutrophil × Monocyte/Lymphocyte.

- **Aggregate index of systemic inflammation (AISI):** Neutrophil × Platelet × Monocyte/Lymphocyte.
- **Neutrophil-to-lymphocyte (NLR) ratio:** Neutrophil/Lymphocyte.
- **Derived neutrophil-to-lymphocyte (dNLR) ratio:** Neutrophil/(WBC - neutrophil).
- **Platelet-to-lymphocyte (PLR) ratio:** Platelet/Lymphocyte.
- **Monocyte-to-lymphocyte (MLR) ratio:** Monocyte/Lymphocyte.
- **Platelet-to-monocyte (PMR) ratio:** Platelet/Monocyte.

The data of included participants were anonymized and recorded in Microsoft Excel for further analysis. The data were analyzed using IBM SPSS v23.0 (Armonk, NY: IBM Corp.).

The chi-square test was used for categorical variables, including the association between xerosis and pruritus or dialysis status. The correlation between xerosis and pruritus severity was evaluated using Spearman's rank correlation coefficient (Rho). Comparisons of inflammatory markers between groups (pruritus vs. no pruritus, dialysis vs. non-dialysis) were conducted using appropriate statistical tests, including independent samples t-test for normally distributed data and Mann-Whitney U test for non-normal distributions. It was determined that at least 28 participants were required to obtain a moderate effect size (d = 0.5) with 95% power and 5% type I error, applying the finite-population correction. A P value < 0.05 was considered statistically significant.

Results

The study included 92 adult patients diagnosed with CKD, of whom 47 (51.1%) had xerosis and/or pruritus. The demographics and clinical characteristics of patients are shown in Table 1. All patients but one with pruritus had both xerosis and pruritus (n = 34, 97.1%). Thirteen patients with xerosis (28%) did not experience pruritus. Xerosis and pruritus were significantly associated (P < 0.001, chi-square statistic X = 47.953). The severity of xerosis and the severity of pruritus were significantly and positively correlated (Rho = 0.454, P < 0.001).

The Effect of Dialysis on Xerosis and Pruritus

Dialysis was administered to 44 patients, accounting for 47.8% of the total cohort. Xerosis was present in 47 (51.1%) patients, while 35 (38%) patients had pruritus. The proportion of dialyzed patients with xerosis was higher than that of non-dialyzed patients (59.6% vs. 39.6%, P = 0.021). Xerosis severity was not associated with dialysis (P = 0.121). Pruritus was similar in dialyzed and non-dialyzed patients (38.6% vs. 37.5%, P = 0.911), and pruritus severity was not associated with dialysis (P = 0.227).

Table 1. The demographics and clinical characteristics of patients

Characteristics	Total (n = 92)
Age, mean (SD)	69.1 (12.8)
Sex, n (%) Female	 46 (50%)
Dialysis, n (%) Yes	 44 (47.8%)
Xerosis, n (%) Yes	 47 (51.1%)
Xerosis severity, n (%) 0 (no xerosis) 1 (mild) 2 (moderate) 3 (severe) 4 (very severe)	 45 (48.9%) 26 (28.3%) 15 (16.3%) 4 (4.3%) 2 (2.2%)
Pruritus, n (%) Yes	 35 (38%)
Pruritus VAS score, median (IQR)	8 (4)
Pruritus severity (VAS), n (%) No pruritus Mild (< 4) Moderate (4 ≤ -< 7) Severe (7 ≤ -< 9) Very severe (≥ 9)	 57 (62%) 7 (7.6%) 4 (4.4%) 13 (14.1%) 11 (11.9%)

SD: standard deviation, VAS: Visual analog scale, IQR: Interquartile range

The Association Between Inflammatory Markers with Pruritus and with Xerosis

White blood cells, neutrophils, lymphocytes, platelets, and monocytes counts were not different between patients with and without xerosis, and there was no significant association between inflammatory markers and xerosis.

White blood cell, neutrophils, lymphocytes, platelets, and monocytes counts were not different between patients with and without pruritus. The median monocyte-to-lymphocyte (MLR) of patients with pruritus was significantly higher than that of those without (P = 0.037) (Figure 1). No other significant association regarding inflammatory markers was observed between the patients with and without pruritus. Pruritus VAS score was significantly correlated with MLR (Rho = 0.206, P = 0.049). The comparison of CRP and inflammatory indices between the patients with and without pruritus is shown in Table 2.

The Association Between Inflammatory Markers with Dialysis Status

White blood cells, neutrophils, lymphocytes, platelets, and monocytes counts showed no significant differences between patients undergoing dialysis and those not receiving dialysis. The median CRP of the patients on dialysis was significantly higher than that of those not on dialysis (P = 0.046).

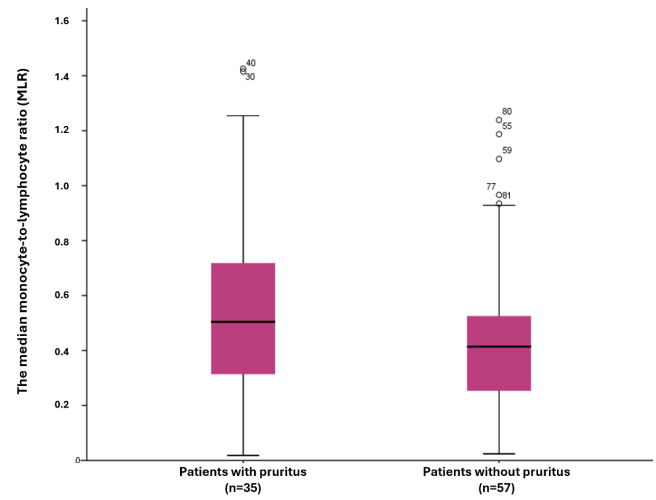

Figure 1. The median monocyte-to-lymphocyte ratio (MLR) was significantly higher in patients with chronic kidney disease-associated pruritus than those without (P = 0.037)

No other significant association with inflammatory markers was observed regarding the dialysis status of the patients (Table 4). The mean MLR levels of patients with pruritus (0.7±0.3) were significantly higher than the mean MLR levels of patients without pruritus (0.4±0.2) among dialyzed patients (P = 0.007).

Discussion

Pruritus and xerosis are the two most common cutaneous manifestations affecting approximately 70% of patients with CKD.[8] The mechanism underlying CKD-associated pruritus remains to be understood. The accumulation of uremic toxins, the release of histamine from mast cells, the imbalance of opioids, the disruption of the epidermal barrier, and the release of inflammatory factors are thought to be primary causes of CKD-associated pruritus.[12] However, it has been recently shown that hyperparathyroidism, hyperphosphatemia, hypercalcemia, and clearance of uremic toxins through adequate dialysis do not correlate with pruritus in CKD. [13] Besides, antihistamines have minimal therapeutic efficacy on pruritus in patients with CKD.[12] Therefore, we investigated the effects of inflammation on CKD-associated cutaneous manifestations, especially on pruritus. We found that pruritus with or without xerosis in patients with CKD was associated with increased MLR levels.

Table 2. Inflammatory markers regarding xerosis and pruritus status

	All (n = 92)	Xerosis (n = 47)	No xerosis (n = 45)	*P* value	Pruritus (n = 35)	No pruritus (n = 57)	*P* value
CRP, median (IQR)	39.6 (90.1)	35.2 (79.1)	48.7 (107.15)	0.303	26.8 (79.1)	56.9 (92.6)	0.335
NLR, median (IQR)	6.3 (5.3)	5.8 (5.7)	3.9 (4.05)	0.082	6.1 (7.1)	4.5 (4.3)	0.064
dNLR, median (IQR)	3.0 (2.4)	3.3 (2.4)	2.4 (2.3)	0.175	3.4 (2.5)	2.8 (2.1)	0.140
PLR, median (IQR)	178.1 (154.5)	188.7 (158.0)	159.5 (148.8)	0.794	188.7 (165.1)	174.8 (143.2)	0.544
MLR, median (IQR)	0.5 (0.4)	0.5 (0.4)	0.4 (0.3)	0.301	**0.5 (0.4)**	**0.4 (0.3)**	**0.037**
PMR, median (IQR)	419.5 (280.8)	397.0 (272.2)	438.6 (255.9)	0.458	377.3 (259)	454.3 (370.7)	0.167
SII, median (IQR)	1121.5 (1517.4)	1398.8 (1828.6)	1080.1 (1260.2)	0.451	1398.8 (2058.1)	1080.1 (1195.8)	0.301
SIRI, median (IQR)	3.1 (3.3)	3.2 (3.9)	2.5 (2.8)	0.371	3.6 (4.9)	2.4 (2.8)	0.079
AISI, median (IQR)	695.2 (1049.8)	676.5 (1142.7)	713.9 (873.1)	0.922	856.3 (1118.3)	527.4 (883.3)	0.325

The significant associations were marked in bold
CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, dNLR: Derived neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, PMR: Platelet-to-monocyte ratio, SII: Systemic immune inflammation response index, SIRI: Systemic inflammatory response index, AISI: Aggregate index of systemic inflammation, IQR: Interquartile range

Xerosis, affecting nearly 85% of individuals with CKD, stands as one of the most common dermatological manifestations associated with pruritus.[14] The present study found that pruritus and xerosis were strongly associated and positively correlated, but 28% of patients with xerosis did not have pruritus. Patients with xerosis relieved of pruritus by moisturizers[15], but some patients with marked xerosis not accompanied by pruritus, suggests that dry skin is probably not an etiologic factor per se, but rather a factor that increases the sensation of pruritus in patients with CKD.

Our study showed no significant association between hemodialysis and pruritus or pruritus severity. Xerosis was more common in patients on dialysis but was not related to the severity of the condition. Numerous studies have evaluated the effect of dialysis on pruritus in CKD patients. According to earlier findings in real-world observational research from The Dialysis Outcomes and Practice Patterns Study (DOPPS), pruritus in patients with CKD occurs in up to 80% of hemodialyzed participants, with approximately 40% of them experiencing moderate to severe itching.[16] A recent large-scale study from DOPPS, including 6256 hemodialysis patients, has shown that optimal dialysis has only slightly reduced the high prevalence of pruritus among dialysis patients.[13] Based on these findings, we conclude that uremic toxins, such as creatinine, urea, nitrogen, and others, are not the only cause of pruritus. However, they may contribute to it in those with CKD.

Inflammatory markers such as o neutrophil-to-lymphocyte (NLR), platelet-to-lymphocyte ratio (PLR) MLR reflect a low-grade inflammatory state in the body and have been commonly evaluated as biomarkers of cardiovascular diseases and malignant conditions.[17] In our study, CKD patients with pruritus had higher MLR values than those without pruritus. However, we did not observe a significant difference in inflammatory

Table 3. Inflammatory markers regarding pruritus status in patients with xerosis

	All (n = 47)	Pruritus (n = 34)	No pruritus (n = 13)	*P* value
CRP, median (IQR)	35.2 (79.1)	30.6 (86.6)	64.7 (72.7)	0.905[a]
NLR, mean (SD)	6.7 (4.4)	7.2 (4.6)	5.4 (3.7)	0.219[b]
dNLR, median (IQR)	3.3 (2.4)	3.5 (2.4)	3.1 (2.0)	0.341[a]
PLR, median (IQR)	188.7 (158.0)	193.8 (169.2)	181.0 (163.0)	0.405[a]
MLR, mean (SD)	0.5 (0.4)	**0.6 (0.4)**	**0.4 (0.2)**	**0.046[b]**
PMR, median (IQR)	397.0 (272.2)	356.2 (263.8)	468.3 (379.1)	0.244[a]
SII, mean (SD)	1575.4 (1301.4)	1740.3 (1433.8)	1143.9 (749.0)	0.162[b]
SIRI, mean (SD)	3.9 (3.2)	4.5 (3.4)	2.5 (1.9)	0.051[b]
AISI, median (IQR)	676.5 (1142.7)	896.5 (1129.1)	414.2 (661.5)	0.101[a]

The significant associations were marked in bold
[a]Independent samples Mann-Whitney U test
[b]Independent samples T-test
CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, dNLR: Derived neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, PMR: Platelet-to-monocyte ratio, SII: Systemic immune inflammation response index, SIRI: Systemic inflammatory response index, AISI: Aggregate index of systemic inflammation, IQR: Interquartile range

Table 4. Inflammatory markers regarding dialysis status

	All (n = 92)	Dialysis (n = 44)	No dialysis (n = 48)	*P* value
CRP, median (IQR)	39.6 (90.1)	**66.4 (104.8)**	**26.3 (71.3)**	**0.046[a]**
NLR, median (SIQR)	6.3 (5.3)	5.9 (5.3)	4.4 (4.4)	0.332[a]
dNLR, median (IQR)	3.0 (2.4)	3.4 (2.8)	2.7 (1.9)	0.220[a]
PLR, median (IQR)	178.1 (154.5)	159.1 (139.9)	202.1 (180.3)	0.270[a]
MLR, median (IQR)	0.5 (0.4)	0.5 (0.4)	0.5 (0.3)	0.725[a]
PMR, median (IQR)	419.5 (280.8)	337.5 (302.2)	438.7 (232.7)	0.088[a]
SII, median (IQR)	1121.5 (1517.4)	1016.2 (1193.9)	1329.5 (1647.5)	0.511[a]
SIRI, median (IQR)	3.1 (3.3)	3.1 (3.0)	3.0 (3.6)	0.737[a]
AISI, median (IQR)	695.2 (1049.8)	520.1 (809.2)	830.2 (1154.6)	0.220[a]

The significant associations were marked in bold
[a]Independent samples Mann-Whitney U test
[b]Independent samples T-test
CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, dNLR: Derived neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, PMR: Platelet-to-monocyte ratio, SII: Systemic immune inflammation response index, SIRI: Systemic inflammatory response index, AISI: Aggregate index of systemic inflammation, IQR: Interquartile range

markers between patients with and without xerosis among CKD patients. When we evaluated the relationship between pruritus and MLR in patients with xerosis only, we found that the MLR of pruritic patients was higher than that of non-pruritic patients. A previous study from Türkiye reported that PLR values were significantly lower in dialysis patients with pruritus compared to those without pruritus. MLR was not evaluated in this study.[18] We found no other study evaluating pruritus and inflammatory markers in CKD patients. A study evaluating pruritus in mycosis fungoides patients showed no relationship between pruritus and MLR.[19]

In a population-based study comparing 3,015 CKD patients with 8,247 non-CKD individuals, MLR was higher in CKD patients. This study also showed that MLR was associated with cardiovascular and all-cause mortality in CKD patients and had the highest predictive value compared to other factors.[20] Patients with moderate to extreme pruritus have also been shown to be at higher risk for death or transfer to hemodialysis.[21] Another large-scale study reported that MLR is a marker that can strongly predict the risk of new-onset CKD.[22] Moreover, MLR was significantly and independently associated with inflammation and disease severity in individuals with CKD.[23] Considering the higher MLR levels in pruritic patients observed in our study, it can be inferred that inflammation plays a significant role in the pathogenesis of pruritus in CKD patients. In order to prevent poor health outcomes and mortality, patients with pruritus and elevated MLR levels should be monitored more closely.

If inflammation is associated with pruritus in CKD patients, why is it only MLR associated with pruritus and not NLR, PLR, or CRP? The elevated levels of MLR in pruritic CKD patients suggest that monocytes may be involved in the mechanism of uremic pruritus. In CKD, monocytes play a significant role in low-grade chronic inflammation. Proinflammatory cytokines like interleukin-1β (IL-1β), tumor necrosis factor-alpha, and IL-6 are secreted by these cells.[24] Upon examining the relationship between dialysis and inflammatory markers, CRP levels were found to be elevated in dialysis patients, but MLR levels were similar between non-dialyzed and dialyzed patients. MLR levels were higher again in dialysis patients with pruritus compared to those without it. In a previous study, a larger proportion of intermediate monocytes (CD14++, CD16+) independently predicted pruritus intensity in patients receiving hemodialysis. The findings imply that uremic pruritus may be related to altered monocytic phenotypes.[25]

Study Limitations

The study had limitations. Since it is cross-sectional and observational, causality cannot be established. The results may not be generalizable due to the small sample size and the study being conducted in a single center. The severity of CKD, comorbidities, and complications such as cholestasis, diabetes, anemia, as well as medications that may cause pruritus other than due to xerosis, may be confounding factors and are not evaluated in this study.

Conclusion

In conclusion, we reported a strong association of pruritus with elevated MLR levels in CKD patients. More structured studies investigating the role of monocytes in CKD-related pruritus are warranted. Monocytes appear to be central players in inflammation, pruritus, and mortality in CKD. Therefore, therapeutic approaches to reduce monocyte activity may be used in the management of CKD-associated pruritus and CKD in general.

Ethics

Ethics Committee Approval: The study received approval from the Non-Interventional Clinical Research Ethics Committee of Uşak University Faculty of Medicine (approval number: 386-386-08, date: 06.06.2024).

Informed Consent: Patients aged 18 years or older with a confirmed diagnosis of CKD, and giving informed consent to participate, were included in the study

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.D.Ö, O.V.Ç, N.İ, Z.A, E.H, Concept: N.D.Ö, O.V.Ç, N.İ, Z.A, E.H, Design: N.D.Ö, O.V.Ç, Data Collection or Processing: N.D.Ö, O.V.Ç, N.İ, Z.A, E.H, Analysis or Interpretation: N.D.Ö, O.V.Ç, N.İ, Literature Search: N.D.Ö, O.V.Ç, N.İ, Writing: N.D.Ö, O.V.Ç.

Conflict of Interest: The authors declared that they have no conflict of interest.

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Original Article

Social Appearance Anxiety and Its Impact on Patients with Verruca Vulgaris: A Comparative Study with Healthy Controls

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Abstract

Aim: Verruca vulgaris, commonly known as warts, is a benign skin condition caused by the human papillomavirus. These lesions can appear on visible parts of the body, leading to concerns about appearance and social interactions. This comparative study seeks to evaluate the social appearance anxiety experienced by individuals afflicted with verruca vulgaris on prominently visible body regions, employing the Social Appearance Anxiety Scale (SAAS) for comparative analysis with healthy counterparts.

Materials and Methods: A group of patients comprising 180 patients aged between 18 to 65 years, diagnosed with verruca vulgaris, alongside 170 healthy controls, participated in the examination. The participants undertook the SAAS, as well as the Hospital Anxiety and Depression Scales; supplementary assessments concerning dermatological quality of life and Visual Analog Scales (VASs) were also administered to the patient group.

Results: The average mean SAAS score for the patient group was 58.47, contrasting with the control group's mean score of 20.92, which signifies a markedly elevated level of anxiety among patients with verruca vulgaris ($P < 0.01$). A noteworthy positive correlation was identified between SAAS and VAS scores ($r = 0.325$, $P < 0.05$).

Conclusion: Visible verruca vulgaris lesions contribute to heightened social appearance anxiety. The findings suggest the need for integrating psychiatric care alongside dermatological treatment to address the psychological impact of the condition.

Keywords: Anxiety, human papillomavirus, skin diseases, verruca

Introduction

Verruca vulgaris, commonly known as warts, is a skin condition caused by the human papillomavirus. These benign lesions predominantly occur on hands, feet, and other visible areas of the body. The prevalence of verruca vulgaris varies, with higher rates observed in immunocompromised individuals and children.[1] Although generally benign, the presence of warts on visible parts can lead to psychological distress, particularly concerning body image and social interactions.[2]

The psychosomatic nature of dermatological conditions such as verruca vulgaris underscores the complex interplay between skin health and mental well-being.[3] Psychological factors like anxiety and depression are known to exacerbate dermatological conditions, which in turn can worsen these psychological symptoms, creating a vicious cycle.[4] Patients with visible skin lesions often experience a decline in self-esteem, leading to social withdrawal and impaired quality of life.[5]

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Social appearance anxiety, defined as the fear of being negatively evaluated based on one's appearance, is a significant concern for individuals with visible dermatological conditions.[6] Despite extensive research on the psychiatric comorbidities associated with skin disorders, there is a paucity of studies specifically focusing on social appearance anxiety in patients with verruca vulgaris.[7]

This research seeks to assess social appearance anxiety among individuals exhibiting conspicuous verruca vulgaris lesions, juxtaposing these findings with those from a healthy control group.[8] Furthermore, the investigation explores the relationship between social appearance anxiety, symptoms of anxiety and depression, the severity of the condition, and the quality of life, as it pertains to dermatological health.[9]

Materials and Methods

This descriptive cross-sectional study was conducted among patients with verruca vulgaris, particularly those with visible lesions, at the Dermatology Department of Van Yüzüncü Yıl University Hospital. The study included volunteers who were aged 18-65 years, literate, and at least primary school graduates. Exclusion criteria included the presence of other psychiatric or skin conditions.

The Social Appearance Anxiety Scale (SAAS), the Hospital Anxiety and Depression (HAD) Scale, the Visual Analogue Scale (VAS), and the Dermatological Quality of Life Index (DLQI) were utilized in the assessment of the patient group. Conversely, the control group filled out the socio-demographic data form, along with the SAAS and HAD scales.

Ethical approval was obtained from the Van Yüzüncü Yıl University Hospital Ethics Committee (approval number: 2020/02-09, date: 21.02.2020). Informed consent was obtained from all participants.

Statistical analysis

Continuous variables were expressed as their mean, standard deviation, minimum, and maximum values, whereas categorical variables were presented as frequencies and percentages. The normal distribution of continuous variables was evaluated employing the Kolmogorov-Smirnov test. Independent t-tests facilitated the comparison of group means, and Pearson correlation analysis was utilized to investigate the interrelations among variables. A statistical significance threshold was established at 5%, and the analyses were performed utilizing IBM SPSS Statistics (Version 21.0; IBM Corp., Armonk, NY, USA).

Results

A total of 180 verruca vulgaris patients (mean age: 32.15±10.89) and 170 healthy controls (mean age: 31.40±11.23) participated in the study. Socio-demographic characteristics are presented in Table 1.

The mean SAAS score in the patient group was 58.47, significantly higher than the control group's mean of 20.92 ($P < 0.01$). While HAD anxiety scores showed no significant difference, HAD depression scores were higher in the control group ($P < 0.01$) (Table 2).

Correlation analysis revealed a significant positive correlation between SAAS and VAS scores ($r = 0.325$, $P < 0.05$), indicating that visible lesions increased social appearance anxiety. No significant correlation was found between SAAS and DLQI scores (Table 3).

Discussion

This study provides significant insights into the psychological impact of verruca vulgaris, particularly in relation to social appearance anxiety.[10] The results indicate that individuals with verruca vulgaris, especially those with visible lesions, experience markedly higher levels of social appearance anxiety compared to healthy controls. These findings align with previous research demonstrating that dermatological conditions, particularly those affecting visible areas, can lead to profound psychological distress and social anxiety.[11]

The mean SAAS score for the patient group was significantly higher than that of the control group, suggesting that the visibility of verruca vulgaris plays a crucial role in exacerbating social anxiety.[12] Similar results have been observed in studies focusing on other visible dermatological conditions, such as acne, psoriasis, and vitiligo, where patients exhibited heightened anxiety related to their appearance.[13] This correlation underscores the pervasive impact of visible skin conditions on patients' psychological well-being, extending beyond mere cosmetic concerns.[14]

Our findings are consistent with previous studies that have identified a positive correlation between the severity of visible lesions and social appearance anxiety. The significant correlation between SAAS and VAS scores in our study suggests that the more visible and severe the lesions, the greater the anxiety experienced by the patients. This is in line with research by Sule Afsar et al.[15], who also reported that patients with more prominent dermatological conditions tend to suffer from higher levels of social anxiety and reduced quality of life. However, unlike some other skin conditions where quality of life is severely impacted, our study did not find a strong correlation between SAAS and DLQI

scores, indicating that while appearance-related anxiety is significant, it may not always translate into broader quality of life measures. This may reflect the specific psychological dynamics of verruca vulgaris, where the primary concern is the social perception of visible lesions rather than functional impairment or physical discomfort.

One noteworthy aspect of our findings is the contrast between the anxiety and depression scores in the patient and control groups. While the SAAS scores were significantly higher in the patient group, the HAD depression scores were actually higher in the control group. Although this result may initially appear unexpected, it highlights the specificity of social appearance anxiety as a distinct psychological construct that does not necessarily correlate with general depression or anxiety levels. This distinction is important for clinical practice, as it suggests that treating verruca vulgaris requires a targeted approach that specifically addresses appearance-related concerns rather than general psychological distress.

The literature on psychosomatic dermatology highlights the bidirectional relationship between skin health and psychological well-being. Psychological stress can exacerbate skin conditions, and in turn, these conditions can worsen psychological symptoms, creating a vicious cycle.[16] Our study adds to this body of knowledge by emphasizing the need for dermatologists to be aware of the potential psychological implications of visible lesions and to consider referring patients for psychological support when necessary. The integration of cognitive-behavioral therapy and other psychosocial interventions into dermatological care has been shown to be effective in managing the psychological burden associated with skin conditions.[17] Given the high levels of social appearance anxiety observed in our study, such interventions could be particularly beneficial for patients with verruca vulgaris.[18]

Furthermore, the results of this study have implications for public health and patient education. There is a need for increased awareness among healthcare providers about the psychosocial impacts of dermatological conditions, particularly those affecting visible areas of the body.[19] Educating patients about the psychological aspects of their condition and providing them with coping strategies can help mitigate the anxiety associated

Table 1. Socio-demographic characteristics of participants

Characteristic	Patient group (n = 180)	Control group (n = 170)
Age (mean ± SD)	32.15±10.89	31.40±11.23
Gender (male/female)	92/88	90/80
Marital Status (single/married)	100/80	95/75
Educational status (primary/high school/university)	60/40/80	65/35/70
Occupation (housewife/unemployed/student/officer)	40/30/70/40	45/25/60/40
Smoking (yes/no)	110/70	105/65
Alcohol (yes/no)	50/130	55/115
Psychiatric history (yes/no)	25/155	30/140

SD: Standard deviation

Table 2. Comparison of SAAS and HAD scores in patient and control groups

Scale	Patient group (mean ± SD)	Control group (mean ± SD)	*P* -value
SAAS	58.47±8.75	20.92±9.45	< 0.001
HAD-A	6.92±2.53	7.11±2.65	0.534
HAD-D	7.23±1.64	8.05±2.27	< 0.001

HAD: Hospital Anxiety and Depression Scale, SAAS: Social Appearance Anxiety Scale, SD: Standard deviation

Table 3. Correlations in the patient group

Variable	SAAS	HAD-A	HAD-D	DLQI	VAS
SAAS	1	0.498**	0.070	0.065	0.325**
HAD-A	0.498**	1	0.122	0.284**	0.250*
HAD-D	0.070	0.122	1	0.009	0.180
DLQI	0.065	0.284**	0.009	1	0.683**
VAS	0.325**	0.250*	0.180	0.683**	1

*$P < 0.05$, **$P < 0.01$
HAD: Hospital Anxiety and Depression Scale, SAAS: Social Appearance Anxiety Scale, VAS: Visual Analogue Scale, DLQI: Dermatological Quality of Life Index

with social appearance concerns.[20] Moreover, public health campaigns aimed at reducing the stigma associated with visible skin conditions could also play a role in alleviating the social anxiety experienced by these patients.[21]

In a recent study, 543 patients with perioral dermatitis, acne, folliculitis, and rosacea in the facial area were compared with 497 healthy volunteers in terms of psychiatric symptoms such as anxiety and depression. Among the compared facial dermatoses, the highest anxiety and depression scores were found in acne patients.[22]

The meta-analysis showed that patients with inflammatory bowel disease experienced a high prevalence of symptoms of anxiety and depression, with approximately one in three patients affected by anxiety symptoms and one in four patients affected by depression symptoms.[23]

There are not many studies demonstrating that verruca vulgaris has a significant negative effect on quality of life. It has been reported that the presence of psychiatric symptoms is a strong determinant of impairment in quality of life in various dermatological diseases.[24,25]

Comparing our results with existing literature, it is evident that verruca vulgaris shares many similarities with other dermatological conditions in terms of its psychological impact. However, the specific nature of social appearance anxiety in verruca vulgaris patients, as revealed by our study, suggests that tailored therapeutic approaches are necessary. Future research should explore the long-term psychological outcomes of patients with verruca vulgaris and the effectiveness of various psychosocial interventions in reducing social appearance anxiety.

Overall, our study underscores the importance of a holistic approach to the treatment of verruca vulgaris that addresses both the physical and psychological aspects of the condition. By recognizing and addressing the social appearance anxiety experienced by patients, healthcare providers can improve treatment outcomes and enhance the overall quality of life for those affected by this common but often distressing condition.

Conclusion

This research emphasizes the significant impact of verruca vulgaris on social appearance anxiety and advocates for a multidisciplinary treatment strategy. By simultaneously addressing the dermatological and psychological dimensions of this condition, it is possible to achieve enhanced health outcomes and a superior quality of life for affected individuals. Subsequent investigations should examine the significance of psychosocial interventions and the potential benefits of incorporating mental health services into the conventional treatment framework for verruca vulgaris.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Van Yüzüncü Yıl University Hospital ethics committee (approval number: 2020/02-09, date: 21.02.2020).

Informed Consent: Informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.T., N.K., F.K., Concept: M.T., N.C., F.K., Design: M.T., N.C., N.K., Data Collection or Processing: F.K., Analysis or Interpretation: M.T., F.K., Literature Search: M.T., N.C., N.K., F.K., Writing: M.T., N.C., N.K., F.K.

Conflict of Interest: The authors declared that they have no conflict of interest.

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Original Article

Risk Factors Associated with Comorbidities and Complications in Patients with Herpes Zoster Ophthalmicus: A Retrospective Analysis

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Abstract

Aim: The incidence of herpes zoster ophthalmicus (HZO) has been increasing in recent years. Although HZO is a self-limiting disease with an excellent response to treatment, it may cause significant neurological and ocular complications. We aim to identify the demographic and clinical characteristics of patients with HZO and determine the risk factors for ocular involvement and postherpetic neuralgia (PHN). Additionally, we investigate how these risk factors might inform early diagnostic and therapeutic interventions, ultimately guiding strategies to prevent HZO-related complications.

Materials and Methods: Eighty-six patients diagnosed with HZO and hospitalized at our institution were evaluated. All patients underwent inpatient follow-up to monitor for potential ocular complications. PHN was defined as either the documented persistent pain or use of analgesic medications three months post-HZO onset.

Results: A total of 86 patients were included, with a mean age of 67.2±13.0 years and a male-to-female ratio of 0.91. Ocular involvement was observed in 57.0% of cases. No significant associations regarding age, sex, immunosuppression status, or Hutchinson's sign were found between patients with and without ocular involvement. However, patients with maxillary or combined maxillary-mandibular branch involvement had a significantly lower risk of ocular complications ($P < 0.001$). PHN occurred in 46.5% of patients and was significantly linked to greater clinical severity ($P = 0.026$) and neurologic symptoms ($P = 0.005$).

Conclusion: Whereas Hutchinson's sign did not predict ocular involvement, involvement of the maxillary and mandibular branches was linked to a reduced risk of ocular complications. Clinical severity was positively correlated with PHN.

Keywords: Herpes zoster ophthalmicus, Hutchinson sign, ocular complications, postherpetic neuralgia, varicella zoster virüs

Introduction

Herpes zoster ophthalmicus (HZO) results from the reactivation of the varicella-zoster virus within the ophthalmic branch of the trigeminal nerve and can cause significant ocular morbidity. Approximately 10-15% of herpes zoster cases involve the ophthalmic division, and nearly half of these develop complications such as keratitis, uveitis, and conjunctivitis.[1,2] In patients with ocular involvement, long-term complications such as postherpetic neuralgia (PHN) may occur, contributing to chronic neuropathic pain. PHN significantly reduces the quality of life, particularly in older patients, often requiring prolonged management.[3] While systemic antiviral therapy has proven essential in reducing HZO-related complications,[1,4] the risk factors for ocular involvement and PHN in HZO are still

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not fully understood. We aim to identify the demographic and clinical characteristics of patients with HZO and determine the risk factors for ocular involvement and PHN. Additionally, we investigate how these risk factors might inform early diagnostic and therapeutic interventions, ultimately guiding strategies to prevent HZO-related complications.

Materials and Methods

Study Design and Patient Selection

In this single-center, retrospective study, we evaluated 86 patients diagnosed with HZO admitted to our institution between 2007 and 2023. Demographic and clinical data were collected from electronic medical records. The inclusion criteria mandated a clinically confirmed diagnosis of HZO, while patients with incomplete medical records or pre-existing ocular disorders were excluded from the study. The retrospective study was approved from the Ethics Committee of University of Health Sciences Türkiye, İstanbul Training and Research Hospital (approval number: 368, date: 25.11.2022).

Data Collection

Collected data included demographic characteristics (age, sex), duration of symptoms prior to hospital presentation, and presence of immunosuppression. Photographic documentation is a part of standard clinical practice at our institution. All hospitalized patients have photographs taken at admission and during their inpatient stay. In this study, these photographs were reviewed to document and verify the presence of clinical severity, periorbital edema, Hutchinson's sign, laterality (right or left-sided involvement), and specific facial area involvement (eyelid and scalp), including maxillary and/or mandibular branch involvement. Clinical severity was classified based on the presence of hemorrhagic and necrotic crusting. Mild cases were defined by minimal or absent crusting, moderate by prominent crusting without significant necrosis, and severe by extensive hemorrhagic and necrotic crust formation. Ocular manifestations and systemic dissemination were recorded. The following were documented: antiviral treatment regimens, neurological symptoms, and systemic markers such as elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels.

Outcome Measures

All patients were closely monitored during hospitalization for the emergence or progression of HZO-related ocular complications through consultations with ophthalmologists. PHN was defined as any persistent pain symptom or the continued use of analgesic medications documented in medical records at least three months after HZO onset.

Primary Outcomes

Incidence of ocular complications: To determine the overall rate of ocular involvement (e.g., keratitis, kerato-uveitis, conjunctivitis) in HZO.

Incidence of PHN: To quantify the prevalence of PHN.

Risk factors for ocular involvement and PHN: To identify demographic, clinical, and treatment-related variables associated with developing ocular complications or PHN.

Secondary Outcomes

Symptom duration and treatment timing: To explore the effect of early vs. delayed presentation on clinical severity, ocular outcomes, and PHN incidence.

Clinical severity, immunosuppression, and neurological symptoms: Investigate the impact of overall clinical severity (e.g., hemorrhagic or necrotic crusting), immunosuppression status, and neurological symptoms on ocular involvement and PHN development.

Treatment regimens: To assess whether the choice or duration of antiviral therapy correlated with ocular involvement or PHN.

Statistical Analysis

All data analyses were conducted using SPSS version 28.0 [IBM Corp., Armonk, NY, United States of America (USA)] with a significance level set at $P < 0.05$. Statistics were computed, including means, standard deviations, medians, minimum and maximum values, frequencies, and percentages. The normality of data distributions was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Depending on the distribution, independent quantitative variables were analyzed using either t-tests or Mann-Whitney U tests. Chi-square or Fisher's exact tests were employed for categorical variables to identify associations. Spearman's correlation analysis was applied to explore relationships between variables of interest.

Results

Demographic and Clinical Characteristics

Eighty-six patients were included in the study, with a mean age of 67.2±13.0 years (30-98 years). Of these patients, 52.3% were female. The duration of symptoms before hospital presentation ranged from 1 to 20 days, with a median of 5 days. Most patients (62.8%) sought medical attention more than three days after symptom onset. Immunosuppression

was present in 14.0% of the patients. Periorbital edema was observed in 88.4% of cases, predominantly ipsilateral (74.4%).

Hutchinson's sign was observed in 24.4%, while 8.1% of patients showed disseminated disease. Elevated ESR and CRP levels were common, with 59.3% and 64.0% of patients showing elevated levels, respectively. Neurological symptoms (headache, transient confusion, ophthalmoplegia, and hypoesthesia) were present in 23.3% of patients. Table 1. Summarizes the demographic and clinical data of the patients diagnosed with HZO.

Primary Outcome Measures

Ocular involvement and its risk factors: Ocular involvement was documented in 57.0% of the patients, with keratitis being the most prevalent manifestation (30.2%), followed by kerato-uveitis (20.9%) and conjunctivitis (5.8%). There were no significant differences in age, sex, symptom duration prior to presentation, immunosuppression, periorbital edema, laterality, Hutchinson's sign, ESR, and CRP level between patients with and without ocular complications ($P > 0.05$). However, individuals with maxillary or combined maxillary-mandibular branch involvement were significantly less likely to experience ocular involvement compared to those with only ophthalmic branch involvement ($P < 0.001$) Table 2 provides a detailed comparison of patients with and without ocular involvement.

PHN and its risk factors: PHN developed in 46.5% of patients. There were no statistically significant differences in age ($P = 0.082$), sex ($P = 0.434$), or symptom duration prior to presentation ($P = 0.286$) between patients with and without PHN. However, PHN was significantly associated with greater clinical severity ($P = 0.026$), with 35.0% of patients in the severe group developing PHN compared to 10.3% in the mild and moderate groups. Additionally, neurological symptoms were markedly more frequent in the PHN group (37.5%) than in the non-PHN group (10.3%) ($P = 0.005$). Elevated ESR and CRP levels were not significantly associated with the development of PHN ($P > 0.05$ for both). Table 3 provides a detailed comparison of patients with and without PHN.

Secondary Outcome Measures

Symptom duration and treatment timing: Most patients (62.8%) presented more than three days after symptom onset (median of five days). There was no statistically significant difference between delayed presentation (> 3 days) and ocular involvement ($P = 0.358$) or PHN incidence ($P = 0.286$).

Clinical severity, immunosuppression, and neurological symptoms: Clinical severity was categorized as mild (26.7%), moderate (46.5%), or severe (26.7%) based on the extent of hemorrhagic or necrotic crusting. Severe clinical involvement was significantly associated with PHN ($P = 0.026$) but not with ocular complications ($P = 0.155$). Immunosuppression did not correlate with either outcome (both $P > 0.05$). Neurological symptoms were more common in the PHN group (37.5% vs. 10.3%, $P = 0.005$), underscoring their potential value as an early indicator of chronic pain risk.

Treatment regimens: All patients received antiviral therapy, predominantly acyclovir (70.9%), for a mean duration of 9.1±2.9 days. Neither the choice of antiviral agent ($P = 0.160$) nor total treatment duration ($P = 0.557$) had a significant impact on ocular complications. Similarly, no significant differences were found in treatment duration ($P = 0.401$) or antiviral choice ($P = 0.212$) between patients with and without PHN.

Discussion

In this cohort of HZO patients, maxillary and mandibular branch involvement emerged as an unexpected factor reducing ocular complications, while classical markers such as Hutchinson's sign were not significant predictors of ocular involvement. This finding diverges from some previous studies[1,5] that emphasize the prognostic role of Hutchinson's sign. It is possible that variations in patient populations, timing of antiviral treatment, or early ophthalmologic consultation influenced our results. Our study also highlights the strong association between PHN development and severe clinical presentation. The presence of hemorrhagic or necrotic crusting may reflect a more aggressive viral reaction, potentially increasing nerve damage and chronic neuropathic pain.

While some studies have reported that HZ and HZO occur more frequently in females than males, our results did not indicate a significant difference in occurrence between sexes.[6-8] Several reports suggest a higher incidence of zoster in immunocompromised states; however, there are limited data regarding the role of immunosuppressive risk factors in developing HZO manifestations.[9-11] In our study, immunosuppression was present in only 14% of patients and was not associated with an increased risk of ocular involvement, PHN, or disseminated disease. Severe manifestations of HZO have been documented more frequently in immunocompromised individuals, such as those with human immunodeficiency virus/acquired immunodeficiency syndrome.[2,12] HZO typically presents as an acute, painful eruption of erythema, vesicles, macules, papules, and blisters around the periorbital region, often accompanied by periorbital edema and ptosis.[5] In our study, 14% of patients also exhibited periorbital edema in the non-involved contralateral eye. Although the underlying cause is unknown, it is thought that bilateral periorbital swelling

Table 1. Demographic and clinical characteristics of patients with herpes zoster ophthalmicus

		Mean ± SD/n(%)
Age		67.2±13.0
Gender	Male	41 (47.7)
	Female	45 (52.3)
Symptom Duration (Days)		5.3±3.2
	≤ 3 days	32 (37.2)
	> 3 days	54 (62.8)
Immunosuppression		12 (14.0)
Malignancy		11 (12.8)
Periorbital edema	None	10 (11.6)
	İpsilateral	64 (74.4)
	Bilateral	12 (14.0)
Hutchinson's sign		21 (24.4)
Involved side	Right	43 (50)
	Left	43 (50)
Eyelid involvement		79 (91.9)
Scalp involvement		56 (65.1)
Maxillary/mandibular involvement	None	59 (68.6)
	Maxillary	18 (20.9)
	Maxillary + mandibular	9 (10.5)
Ocular involvement		49 (57.0)
	Conjunctivitis	5 (5.8)
	Keratitis	26 (30.2)
	Keratouveitis	18 (21.0)
Onset of ocular involvement (days)		6.0±3.8
Dissemination		7 (8.1)
Neurological symptom		20 (23.3)
Postherpetic neuralgia		40 (46.5)
Clinical severity	Mild	23 (26.7)
	Moderate	40 (46.5)
	Severe	23 (26.7)
Erythrocyte sedimentation rate	Normal	30 (34.9)
	High	51 (59.3)
C-reactive protein	Normal	28 (32.6)
	High	55 (64.0)
Antiviral treatment	Acyclovir	61 (70.9)
	Valacyclovir	14 (16.3)
	Acyclovir + valacyclovir	8 (9.3)
	Brivudine	1 (1.2)
	Acyclovir + brivudine	2 (2.3)
Duration of antiviral treatment (days)		9.1±2.9
Length of hospitalization (days)		9.2±3.3

Min.: Minimum, Max.: Maximum, SD: Standard deviation, PHN: postherpetic neuralgia

Table 2. Risk factors for ocular involvement in HZO

		Ocular involvement (-) (n = 37) Mean ± SD/n (%)	Ocular involvement (+) (n = 49) Mean ± SD/n (%)	*P*
Age		65.7±13.0	68.3±13.1	0.370[t]
Gender	Male	18 (48.6)	23 (46.9)	0.875[X²]
	Female	19 (51.4)	26 (53.1)	
Symptom duration (days)		5.5±2.8	5.2±3.6	0.358[m]
	≤ 3 days	12 (32.4)	20 (40.8)	0.426[X²]
	> 3 days	25 (67.6)	29 (59.2)	
Immunosuppression		5 (13.5)	7 (14.3)	0.919[X²]
Malignancy		5 (13.5)	6 (12.2)	0.862[X²]
Hutchinson's sign		11 (29.7)	10 (20.4)	0.319[X²]
Maxillary/mandibular involvement	None	16 (43.2)	43 (87.8)	**0.000**[X²]
	Maxillary	14 (37.8)	4 (8.2)	
	Maxillary + mandibular	7 (18.9)	2 (4.1)	
Dissemination		5 (13.5)	2 (4.1)	0.113[X²]
Clinical severity	Mild	11 (29.7)	12 (24.5)	0.155[X²]
	Moderate	13 (35.1)	27 (55.1)	
	Severe	13 (35.1)	10 (20.4)	
Neurological symptom		9 (24.3)	11 (22.4)	0.838[X²]
Postherpetic neuralgia		19 (52.8)	21 (48.8)	0.727[X²]
Erythrocyte sedimentation rate	Normal	17 (48.6)	13 (28.3)	0.061[X²]
	High	18 (51.4)	33 (71.7)	
C-reactive protein	Normal	10 (27.8)	18 (38.3)	0.315[X²]
	High	26 (72.2)	29 (61.7)	
Duration of antiviral treatment (days)		8.8±2.4	9.4±3.2	0.557
Length of hospitalization (days)		8.5±3.2	9.7±3.3	0.094[m]

[t]: Independent sample t-test, [m]: Mann-whitney u test, [X²]: Chi-square test (Fisher's exact test)
HZO: Herpes zoster ophthalmicus, SD: Standard deviation

is usually due to gravitational edema rather than the spread of infection to the opposite side of the face.[13] A minority of patients present with only ophthalmic symptoms and no skin rash, suggesting that the risk of ophthalmic complications may not be directly related to the severity of the skin rash.[14,15] Keratitis and conjunctivitis have also been reported as common ocular manifestations of HZO in previous studies.[16-19] Our study's ocular involvement rates were similar to those of previous studies. Initiating systemic antiviral therapy within the first 72 hours is associated with less severe ocular features.[8] The average duration from onset of symptoms to examination by an ophthalmologist was 4.0±2.3 days in one study.[20] In our study, the time of ocular involvement was 6.0±3.8 days. Although the timing of ophthalmologic consultations has not been widely documented, one study found an average duration of approximately five days from rash onset to clinical presentation and subsequent referral to an ophthalmologist.[21] Another analysis of a USA claims database showed that 75.8% of patients consulted an ophthalmologist within seven days of receiving an HZO diagnosis.[7] Our study underscores the crucial role of ophthalmologic consultation, which was requested for all patients at the onset of treatment. This early involvement ensures comprehensive care and better outcomes for patients. Hutchinson's sign (cutaneous involvement of the tip of the nose), indicating nasociliary involvement, is a strong predictor of ocular complications in HZO.[22] However, our study did not find a significant association between Hutchinson's sign and ocular involvement, possibly due to patient characteristics or diagnostic and treatment timing variations. Furthermore, our findings showed no significant differences in ocular outcomes between patients treated with valacyclovir and those treated with acyclovir, consistent with studies suggesting similar efficacy between these agents.[23] In our study, patients started antiviral treatment early. A cohort study conducted in the USA, involving numerous cases of HZO, found that nearly 60% of patients initiated antiviral treatment within seven days of their diagnosis diagnosis.[7] In our study, we found that 37.2% of patients initiated antiviral treatment within 72 hours of symptom onset, while 62.8% began treatment after this period, with acyclovir being the most frequently

Table 3. Risk factors for postherpetic neuralgia in HZO

		PHN (-) (n = 39) Mean ± SD/n (%)	PHN (+) (n = 40) Mean ± SD/n (%)	P
Age		69.3±13.4	64.1±12.9	0.082[t]
Gender	Male	20 (51.3)	17 (42.5)	0.434[X²]
	Female	19 (48.7)	23 (57.5)	
Symptom duration (days)		5.1±3.4	5.8±3.3	0.286[m]
	≤ 3 days	12 (32.4)	20 (40.8)	0.432[X²]
	> 3 days	25 (67.6)	29 (59.2)	
Immunosuppression		4 (10.3)	7 (17.5)	0.352[X²]
Malignancy		4 (10.3)	6 (15.0)	0.526[X²]
Ocular involvement	None	17 (43.6)	19 (47.5)	0.938[X²]
	Conjunctivitis	2 (5.1)	3 (7.5)	
	Keratitis	12 (30.8)	11 (27.5)	
	Keratouveitis	8 (20.5)	7 (17.5)	
Maxillary/mandibular involvement	None	26 (66.7)	26 (65.0)	0.546[X²]
	Maxillary	10 (25.6)	8 (20.0)	
	Maxillary + mandibular	3 (7.7)	6 (15.0)	
Dissemination		4 (10.3)	1 (2.5)	0.157[X²]
Clinical severity	Mild	12 (30.8)	11 (27.5)	**0.026**[X²]
	Moderate	23 (59.0)	15 (37.5)	
	Severe	4 (10.3)	14 (35.0)	
Neurological symptom		4 (10.3)	15 (37.5)	**0.005**[X²]
Erythrocyte sedimentation rate	Normal	16 (44.4)	13 (33.3)	0.324[X²]
	High	20 (55.6)	26 (66.7)	
C-reactive protein	Normal	11 (28.9)	13 (33.3)	0.678[X²]
	High	27 (71.1)	26 (66.7)	
Duration of antiviral treatment (days)		8.8±2.3	9.4±2.9	0.401[m]
Length of hospitalization (days)		8.6±3.2	9.5±3.2	0.183[m]

[t]: Independent sample t-test, [m]: Mann-whitney u test, [X²]: Chi-square test (Fisher's exact test)
HZO: Herpes zoster ophthalmicus, SD: Standard deviation

used antiviral agent (70.9%). The mean duration of antiviral therapy was 9.1±2.9 days, with no significant differences in treatment duration between those with ocular involvement or without it, or with PHN or without it. Intravenous acyclovir (10-15 mg/kg every 8 hours, adjusted based on creatinine clearance) is recommended for disseminated zoster, severe HZO with ocular involvement, and central nervous system zoster. At the same time, oral valacyclovir (1 g three times daily) is indicated for uncomplicated zoster and HZO without ocular involvement. Brivudine and famciclovir also serve as alternative treatment options.[24] Oral valacyclovir is as effective as intravenous acyclovir, potentially offering cost savings due to reduced hospitalization rates.[25] Clarification is needed on the total treatment duration, especially for immunocompromised patients with zoster or those with visceral or ocular involvement. PHN, the most common complication of varicella-zoster virus reactivation, is characterized by chronic, often refractory neuropathic pain persisting over three months after the HZ outbreak.[26] PHN prevalence varies between 5% and 30% depending on the study design and the specific population studied.[27] In some studies, age is a significant risk factor for PHN, along with other factors such as female sex, increased severity of prodromal or acute zoster pain, premorbid functional status, immunocompromised condition, and involvement of the head and neck regions.[28-30] Our study observed no significant differences between patients with and without PHN regarding age, sex, and immunosuppression. However, PHN was significantly associated with the clinical severity of HZO, indicating that more severe cases may require closer monitoring for potential chronic pain development. Elevated ESR and CRP were common findings, with 59.3% and 64.0% of patients, respectively, showing elevated levels. However, in our study, increased acute phase reactants were not associated with ocular involvement, PHN development, or treatment response. Limited data exist on the relationship between elevated acute phase reactants and clinical features, such as treatment response, and complication development in HZO.

Study Limitations

The retrospective nature of this study and its relatively small sample size presents limitations; however, the photographic documentation of cutaneous and ocular findings, conducted for every inpatient at our center, allowed us to verify each lesion's evolution and better correlate clinical severity with subsequent outcomes. This approach adds an objective component to the retrospective review, reducing potential errors in data interpretation. Additionally, none of our patients had received the zoster vaccine prior to infection, which prevented us from assessing its potential protective role in HZO or PHN. Furthermore, no follow-up data were available for recurrence, limiting our insights into long-term outcomes.

Conclusion

In conclusion, HZO is a self-limiting disease that responds well to antiviral treatment, but follow-up and management are critical in neurological and ophthalmological complications. In this cohort of HZO patients, maxillary and mandibular branch involvement emerged as an unexpected factor reducing ocular complications, while classical markers such as Hutchinson's sign were not significant predictors of ocular involvement. Larger, prospective studies are warranted to confirm these findings and to investigate the long-term implications of maxillary-mandibular involvement in HZO, as well as the correlation between clinical severity and PHN. Most studies of HZO are conducted by ophthalmologists. Therefore, more data are needed on HZO patients without ocular involvement. More studies involving dermatologists in relation to skin or laboratory findings with predictive value for developing complications associated with HZO are also needed.

Ethics

Ethics Committee Approval: The study received approval from the Ethics Committee of University of Health Sciences Türkiye, İstanbul Training and Research Hospital (approval number: 368, date: 25.11.2022).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: E.B.A., A.E.K.A., V.M., Design: E.B.A., B.B.D., A.K.P., M.S.G., Data Collection or Processing: B.B.D., V.M., M.S.G., Analysis or Interpretation: E.B.A., B.B.D., A.E.K.A., Literature Search: E.B.A., A.K.P., Writing: E.B.A., A.E.K.A.

Conflict of Interest: The authors declare no conflicts of interest.

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Original Article

The Evolution of Tzanck Smear Publications: A Bibliometric Analysis with Research Trends and Global Productivity

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Abstract

Aim: Tzanck smear is a diagnostic tool where the structural characteristics of cells are examined under microscope after undergoing various staining procedures. It is a cost-effective and reliable application that aids clinicians in the diagnostic process in many fields, particularly dermatology. Bibliometric analysis is an methodology that visualizes study topics, authors, countries, and trends in a scientific field, accompanied by numerical data. This study presents a bibliometric analysis of the Tzanck smear literature.

Materials and Methods: Web of Science database was used for literature search; VOSviewer and Biblioshiny software were preferred for bibliometric analysis.

Results: According to the bibliometric data obtained, herpes and pemphigus group diseases have been the central focus of Tzanck smear studies. Recently, while these two topics have maintained their trend, there has been an increase in Tzanck smear publications related to the Monkeypox virus. The leading authors in terms of publication count are Durdu M, Seckin D, and Folkers E, while the most cited authors are Durdu M, Leonardi CL, and Nahass GT. The leading countries in publishing studies on Tzanck smear are the United States, India, and Türkiye. Journals receiving the most publications and citations on Tzanck smear include the Journal of the American Academy of Dermatology, International Journal of Dermatology, Indian Journal of Dermatology, Venereology and Leprosy, Journal of the American Medical Association, and Archives of Dermatology.

Conclusion: In this study, an attempt was made to create quantitative maps of studies conducted on the topic of Tzanck smear. This study fills an important gap in the literature by representing the first comprehensive bibliometric analysis specifically focused on the topic of Tzanck smear. A review of the literature shows that researchers, countries, and journals have demonstrated varying trends regarding Tzanck smear over the years. The statistical evaluation of these trends through bibliometric analysis can provide a roadmap for researchers planning to work on this topic when designing their studies.

Keywords: Tzanck smear, cytodiagnosis, bibliometric, herpes simplex, pemphigus, skin neoplasms

Introduction

Cytology is a method based on the examination of the characteristic morphological features of cells. It is a diagnostic tool beneficial for the early diagnosis and treatment of various diseases.[1] Although its first use dates back to the mid-19th century, its application in dermatology was initiated by Arnault Tzanck in 1947, and subsequently, its uses in the field of dermatology began to be referred to as the "Tzanck smear test."[2] The Tzanck smear test offers numerous advantages, being simple, rapid, reliable, inexpensive, repeatable, without requiring anesthesia, and painless. Therefore, it is one of the ideal diagnostic methods clinicians can resort to in the process for appropriate patients.[3] Bibliometric analysis is an analytical method used to obtain formal and quantitative data on the current state of a field, facilitating the tracking of academic trends through visualization. Through these analyses, quantitative findings are obtained regarding country, author, university, and journal productivities related to the specified topic, weak and strong sub-research areas, collaboration networks, literature gaps, and potential opportunities for future research.[4,5]

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This study aimed to summarize the Tzanck smear literature between 1983 and 2024 using bibliometric analyses. The study thereby examines the trends, author and country tendencies, prominent or overlooked aspects, and scrutinizes the literature in this field.

Materials and Methods

In this study, the Web of Science database was used for literature search, and VOSviewer, and Biblioshiny software were preferred for bibliometric analysis. On March 14, 2025, a search was conducted in Web of Science using the keyword "Tzanck smear" with "all fields" selected. A total of 182 publications were retrieved, with the oldest from 1983 and the newest from 2024. The retrieved data were analyzed through author-citation-journal-country, and keyword analyses. The threshold values and filtering criteria used in the analyses were determined as follows: author co-authorship analysis: minimum (min.) 2 publications and at least 1 citation; citation analysis: min. 2 publications and at least 1 citation; citation analysis: min. 2 publications and at least 1 citation; citation analysis: journals with at least 1 citation; co-citation analysis: min. 5 citations.

The clustering analysis used the LinLog/modularity-based algorithm of VOSviewer software, which is the VOSviewer default. It creates clusters based on the density of connections between nodes (e.g., authors, countries, or keywords). Analyses were visualized through network maps where node size represents volume (e.g., publications or citations) and color indicates clustering. Temporal trends were visualized using color gradients from purple (older) to yellow (newer).

Results

The study included 134 journal articles, 25 editorial materials, 9 book chapters, 7 review articles, and 7 meeting abstracts. In terms of disciplines, the vast majority of studies belonged to dermatology (107), followed by internal medicine (19), pathology (19), medical laboratory technology (13), infectious diseases (11), experimental medicine and research (7), immunology (7), pediatrics (6), microbiology (6), and surgery (6).

Most Productive Authors in the Field of Tzanck Smear

In the analysis conducted on the Web of Science database using the keyword "Tzanck smear" with "all fields" selected, the top 3 most productive authors, ranked by publication count, were identified as Durdu M. (30 publications), Seckin D. (7 publications), and Folkers E (6 publications). The 10 most productive authors are shown in Figure 1.

Most Productive Countries in the Field of Tzanck Smear

In the analysis conducted on the Web of Science database using the keyword "Tzanck smear" with "all fields" selected, and based on the country of origin of the publications (determined by the corresponding author), the top 3 most productive countries were identified as the United States of America (USA), India, and Türkiye. The productivity of countries is depicted in Figure 2.1 and Figure 2.2, while the total number of publications in the Tzanck smear literature by year is shown in Figure 2.3.

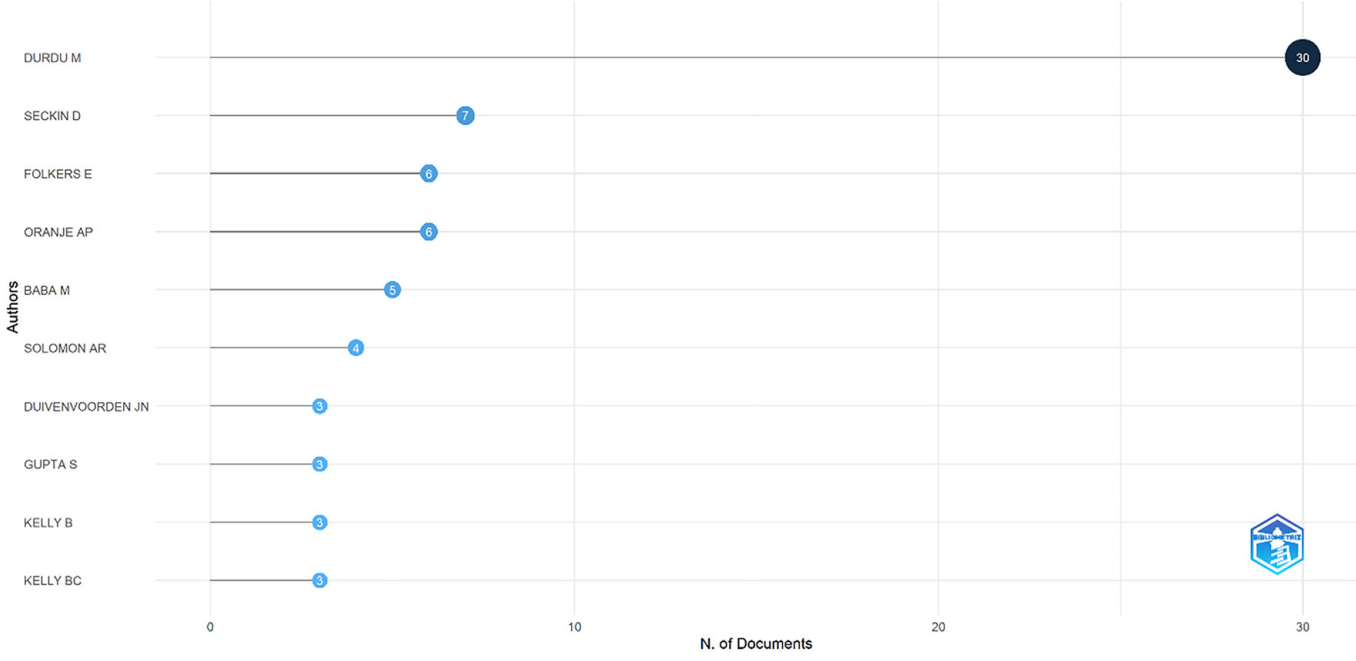

Figure 1. The 10 most productive authors in the Field of Tzanck smear

Co-authorship Analysis

According to the co-authorship analysis, a network map was created using a min. criterion of 2 publications and at least 1 citation to identify authors with the most connections and collaborations. The analysis of authors with the most connections revealed 46 authors grouped into 17 distinct clusters, with a total of 55 links. When examined by year, it is noteworthy that Folkers et al.[7] engaged in co-authorship in the early publications within the Tzanck smear literature[6], while Noormohammadpour et al.[8] have co-authored more recent publications (Figure 3).

Author Citation Analysis

To identify citation networks, a network map for author citation analysis was generated using the criteria of a min. of two publications and at least one citation. The analysis, conducted on 397 interconnected authors, identified 12 clusters, 5386 links, and a total link strength of 10455. The most cited authors were Durdu M. with 259 citations, Leonardi CL with 152 citations, and Nahass GT with 152 citations. According to total link strength, the top 3 authors were Durdu, M., Baba, M., and Seckin M. (Figures 4.1 and 4.2).

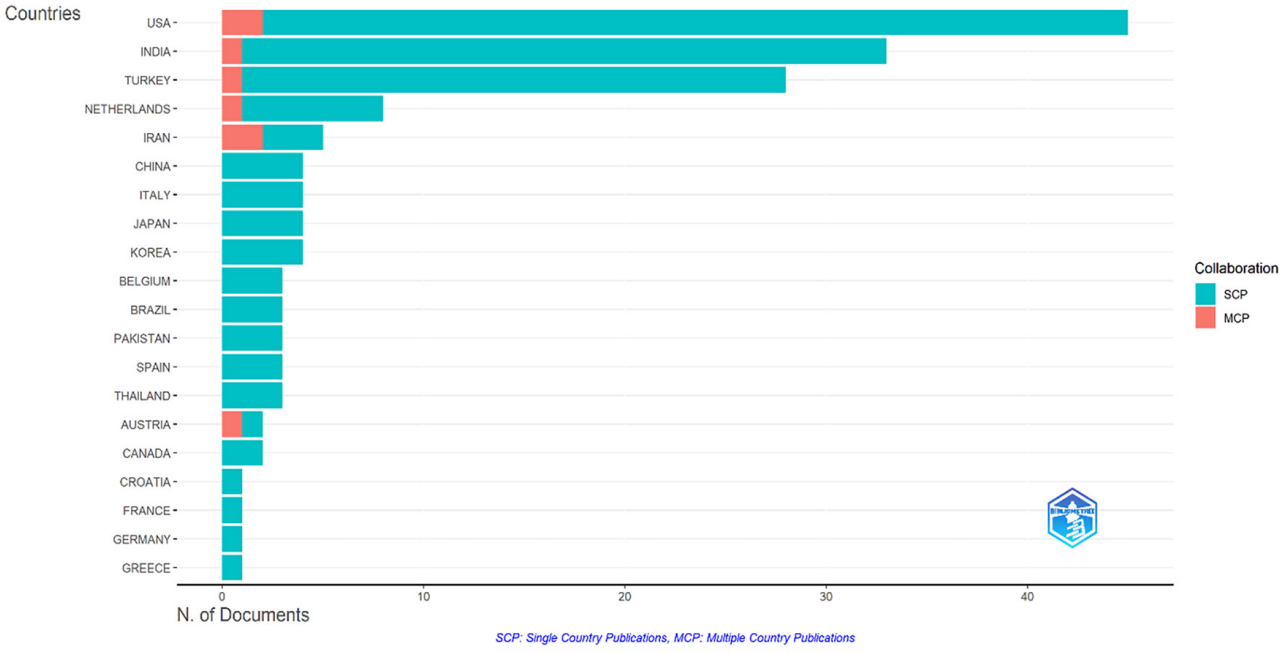

Figure 2.1. Most productive countries in the field of Tzanck smear
USA: United States of America, SCP: Secure copy protocol, MCP: Microsoft certified professional

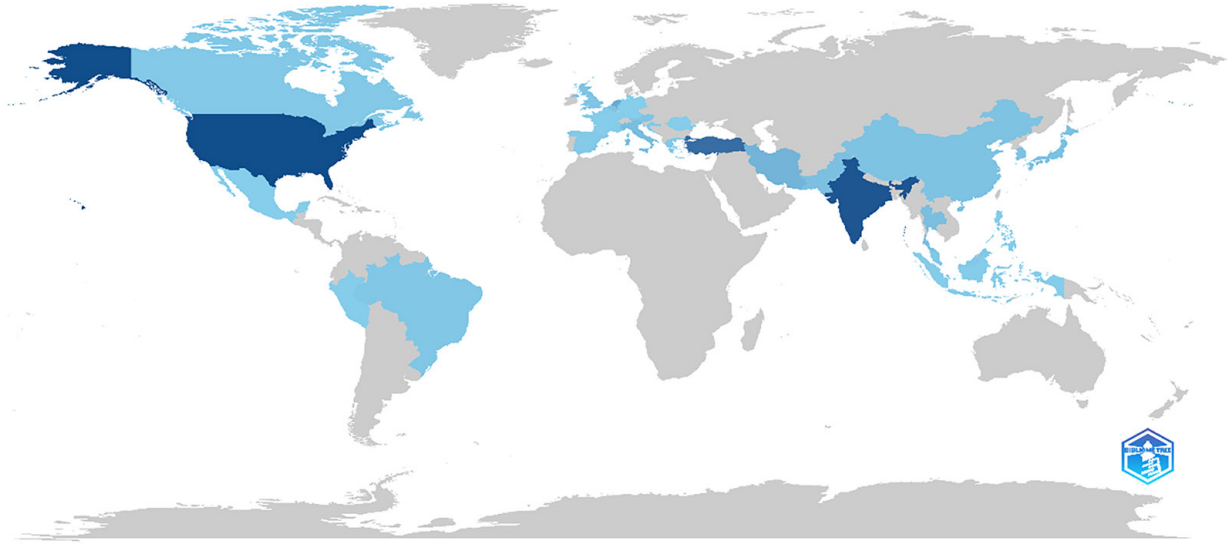

Figure 2.2. Most productive countries in the field of Tzanck smear (map visualization)

Country Citation Analysis

A network map of the citations received by publications according to their source countries was created. The analysis was conducted on 14 interconnected countries, with the requirement that a country must have published at least 2 works and received at least 1 citation. This identified 5 clusters, 32 links, and a total link strength of 177. The most cited countries were the USA (795 citations), Türkiye (270 citations), and India (196 citations). In terms of total link strength, the USA and Türkiye were followed by Italy. The ranking by total number of published works was the USA (47 publications), India (34 publications), and Türkiye (30 publications) (Figures 5.1 and 5.2).

Publication Citation Analysis

To create a network map of citations received by publications, an analysis was conducted on 100 interconnected publications, each having received at least 1 citation. This identified 15

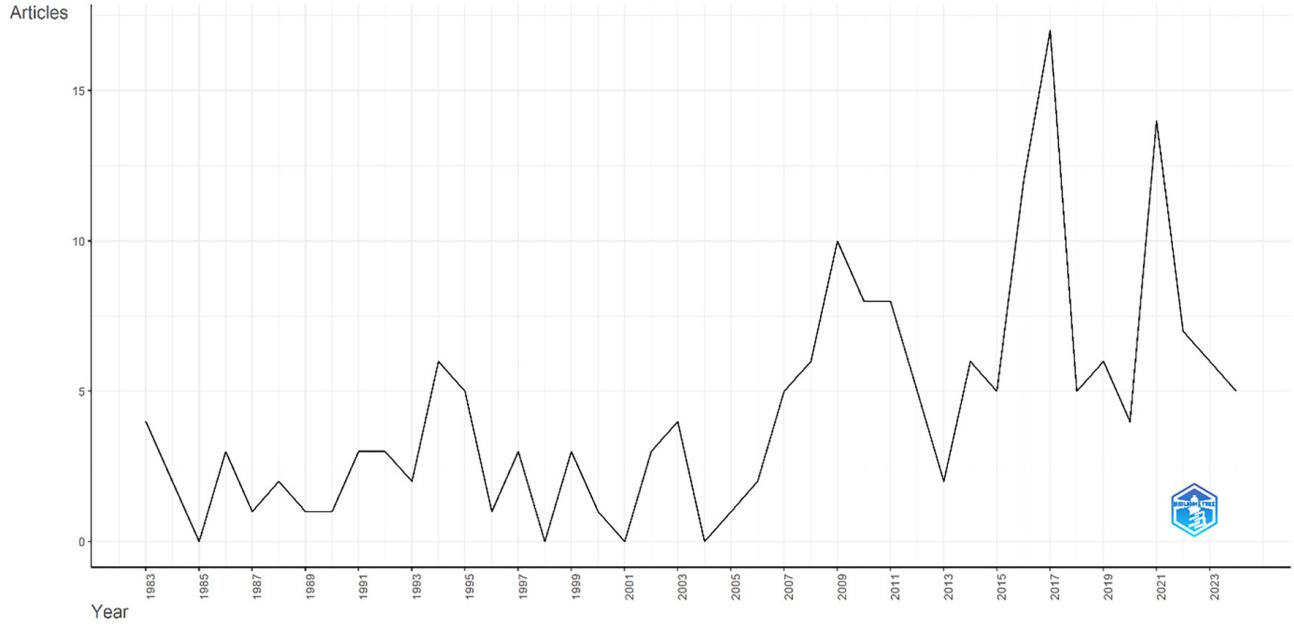

Figure 2.3. A line chart representing the yearly publication trends. Peaks observed in 2009, 2017, and 2022 reflect surges in academic interest, possibly linked to clinical or diagnostic developments

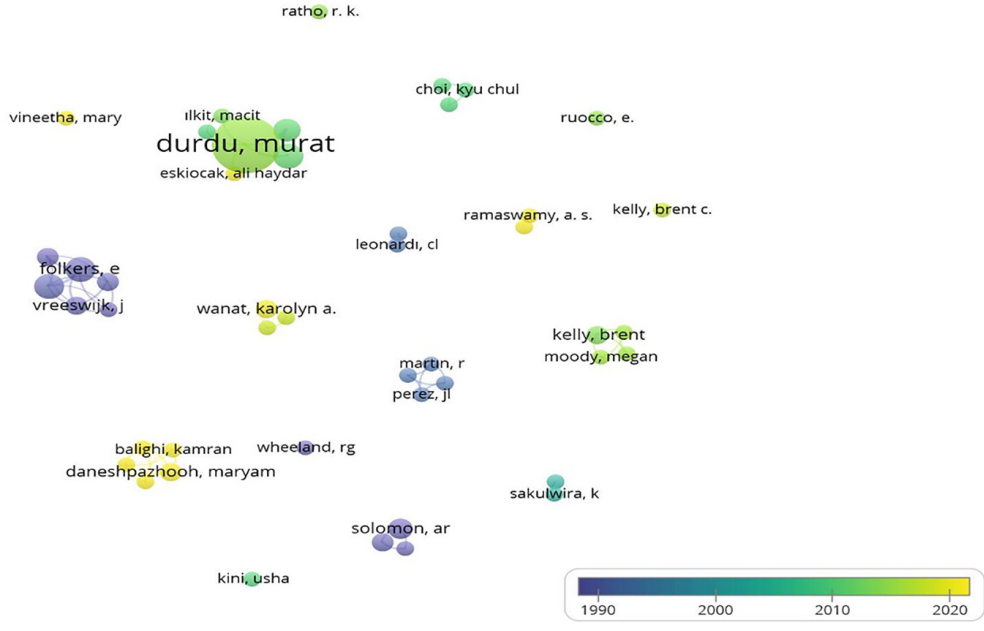

Figure 3. Network visualization showing co-authorship links among authors who have published at least two articles and received at least one citation. Each cluster indicates a group of closely collaborating researchers. Color gradients from purple to yellow represent temporal evolution, with yellow being more recent

clusters and 291 links. The top 3 most cited publications were Nahass et al.[9] (215 citations), Durdu et al.[10] (167 citations) and Solomon et al.[11] (153 citations). In terms of total link strength, the top 3 publications were Durdu et al.[10], Eryılmaz et al.[12] and Solomon et al.[13] (Figure 6).

Source (Journal) Citation Analysis

To create a network map for source (journal) citation analysis, an analysis was conducted on 20 interconnected journals that had published articles on Tzanck smear, with a criterion of at least 1 citation received by articles within them. The analysis identified 7 clusters and 47 links. The top 3 journals publishing the most articles on Tzanck smear were the Journal of the American Academy of Dermatology (22 publications), International Journal of Dermatology (11 publications), and Indian Journal of Dermatology, Venereology and Leprosy (7 publications). When compared by citation counts, the journals receiving the most citations for articles on this topic were the Journal of the American Academy of Dermatology (307 citations), Journal of the American Medical Association (JAMA) (199 citations), and Archives of Dermatology (159 citations). According to the link strength analysis, calculated based on the co-citation of sources (journals) within the same article, the three strongest journals were the Journal of the American Academy of Dermatology, International Journal of Dermatology, and JAMA (Figure 7).

Keyword Analysis

In the analysis of keywords used by authors, a total of 227 keywords were identified, forming 689 links within 30 clusters. The most frequently used keywords in publications related to Tzanck smear were "Tzanck smear" (28 occurrences), "cytology" (18 occurrences), "pemphigus" (10 occurrences), and "acyclovir" and "herpes zoster" (6 occurrences each). In terms of total link strength, these terms also ranked highest in the same order (Figures 8.1, 8.2 and 9).

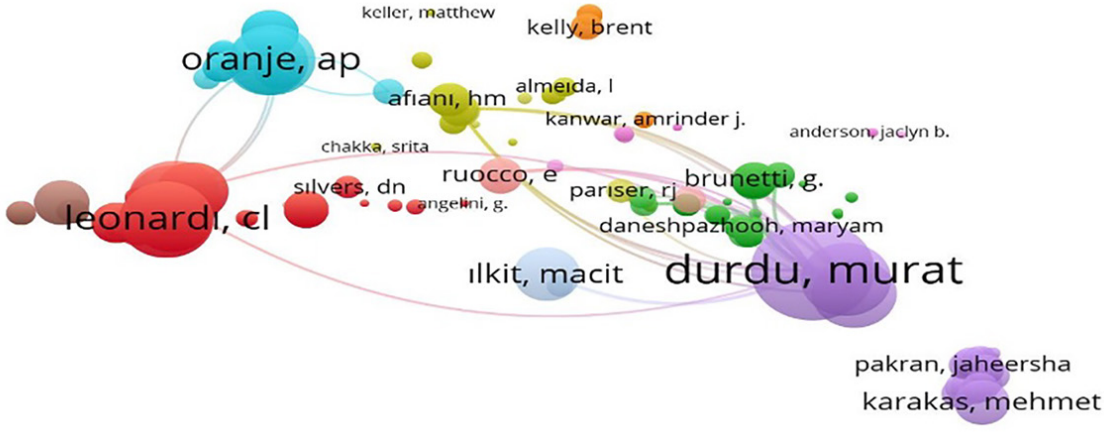

Figure 4.1. This figure shows citation relationships among the most cited authors in the Tzanck smear literature. Node size corresponds to citation volume, and link strength reflects shared citation patterns, helping identify key influencers in the field

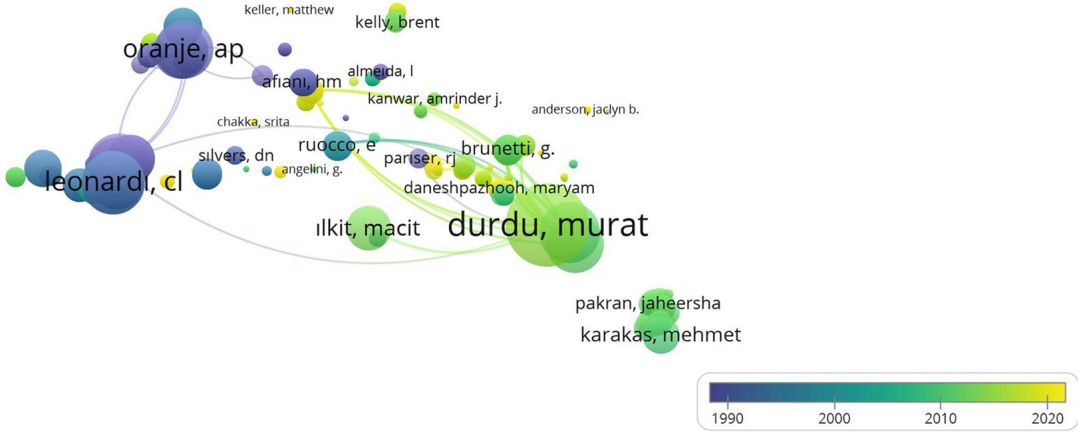

Figure 4.2. Same as Figure 5.1 but color-coded based on the year of most cited work. This allows assessment of which influential authors emerged early or more recently

Author Bibliographic Coupling Analysis

Bibliographic coupling occurs when two independent sources cite a common work/author.[14] For the bibliographic coupling analysis, a criterion of having published at least 2 works and having received at least 1 citation was selected. The analysis, conducted on 46 interconnected authors, yielded 7 clusters, 525 links, and a total link strength of 8392. Authors with the highest bibliographic coupling (measured by total link strength) were Durdu M (2540 total link strength; 259 total citations), Leonardi CL (166 total link strength; 152 total citations), and Nahass GT (166 total link strength; 152 total citations) (Figure 10).

Author Co-Citation Analysis

Co-citation is the frequency with which two documents are cited together by other documents.[15] With a min. co-citation count of 5, the analysis conducted on 50 authors identified a total of 6 clusters, 556 links, and a total link strength of 2441. The most co-cited authors were Durdu M (98 co-citations), Solomon AR (63 co-citations), and Ruocco V (48 co-citations) (Figure 11).

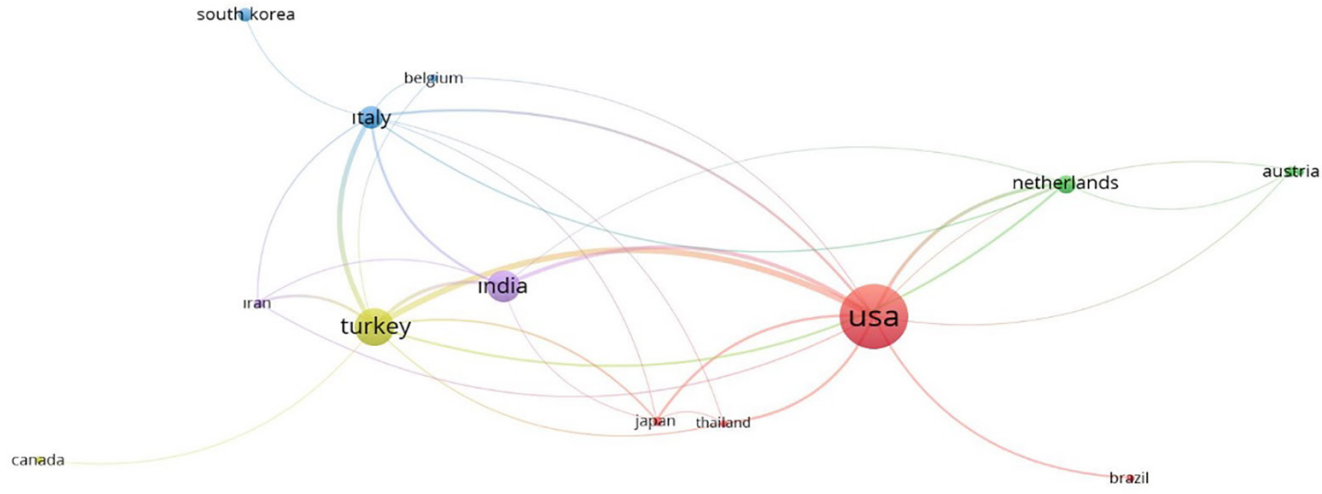

Figure 5.1. Displays how countries cite each other's work in the Tzanck smear literature. Node size reflects citation count received, links indicate citation connections. The USA, Türkiye, India appear as central players
USA: United States of America

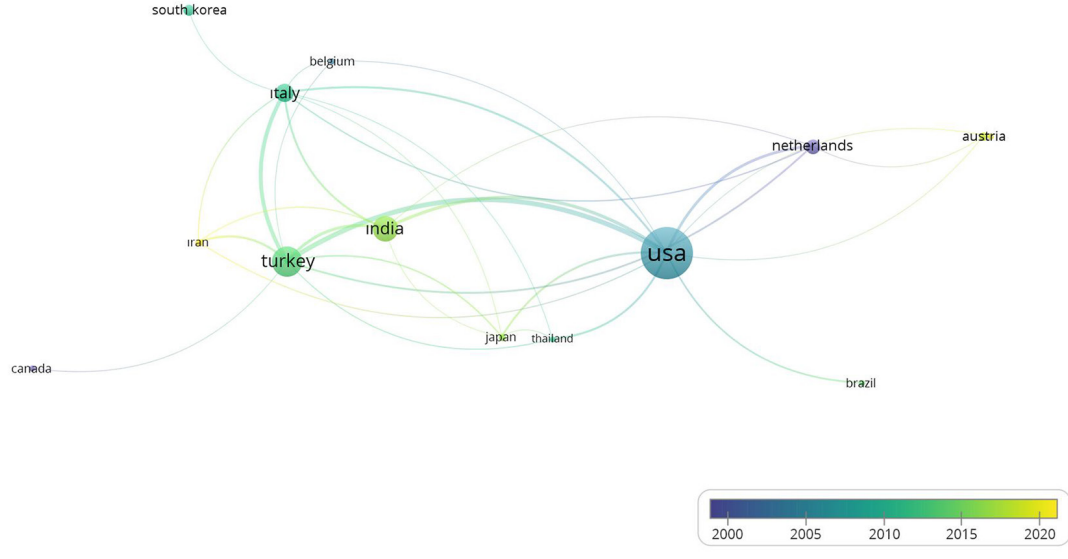

Figure 5.2. Color gradient indicates the chronological distribution of country citations. It helps understand which countries contributed earlier and which became active more recently
USA: United States of America

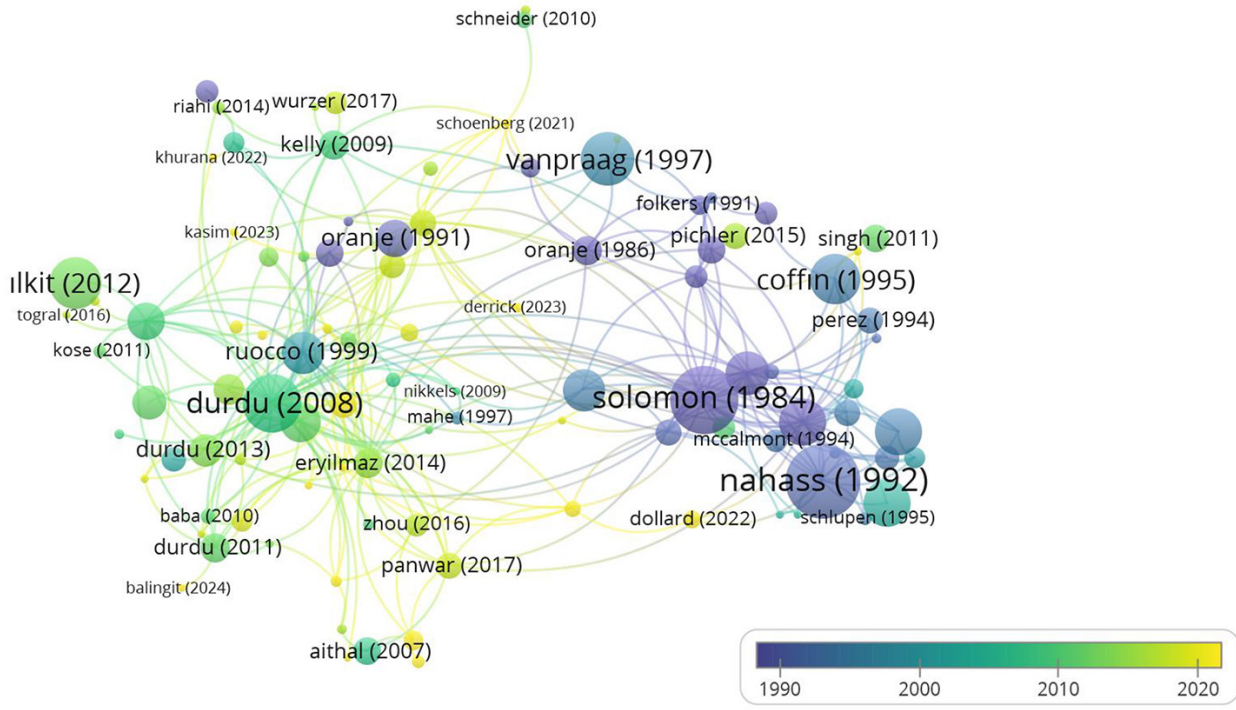

Figure 6. Network visualization of 100 publications with at least one citation. Larger nodes indicate more frequently cited studies. Clusters highlight thematic or topical groupings

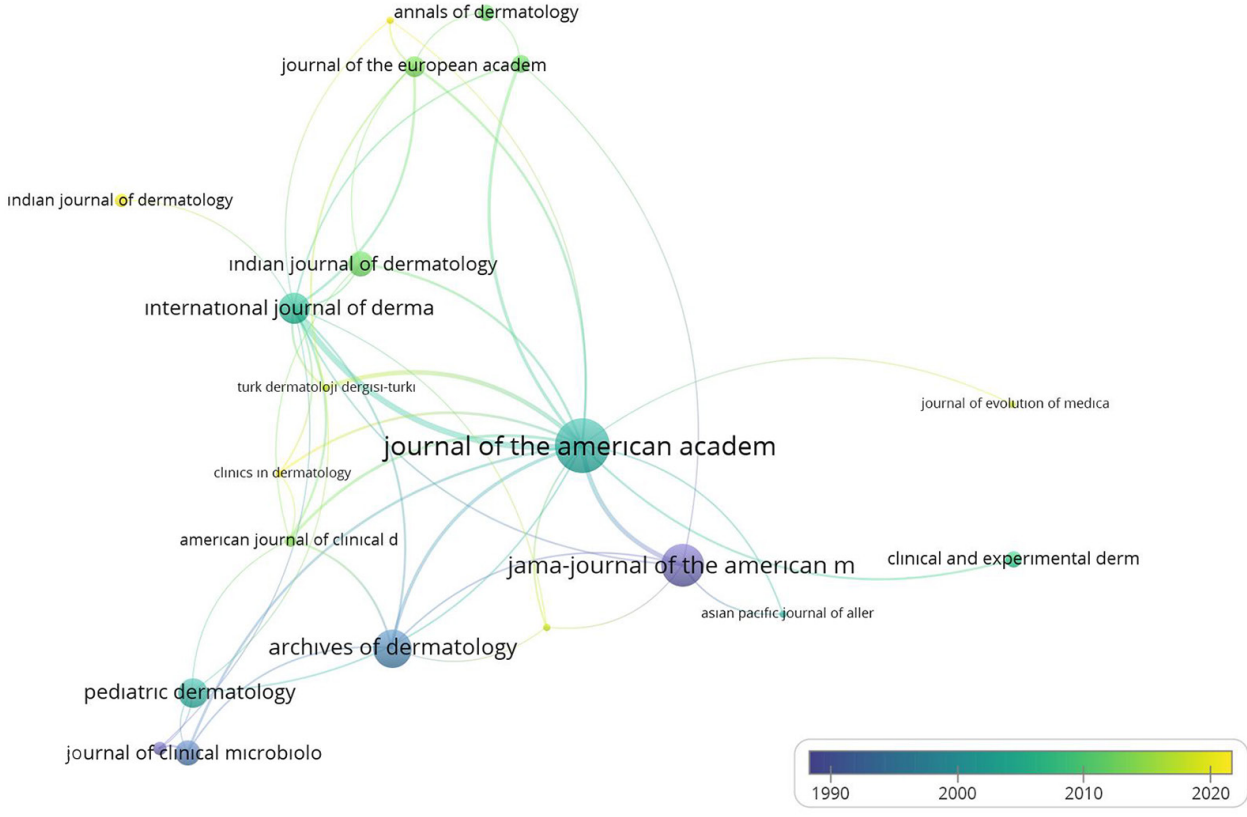

Figure 7. This figure maps inter-journal citation relationships based on co-citation frequency. Journals like Journal of the American Academy of Dermatology (JAMA), and International Journal of Dermatology appear as central nodes

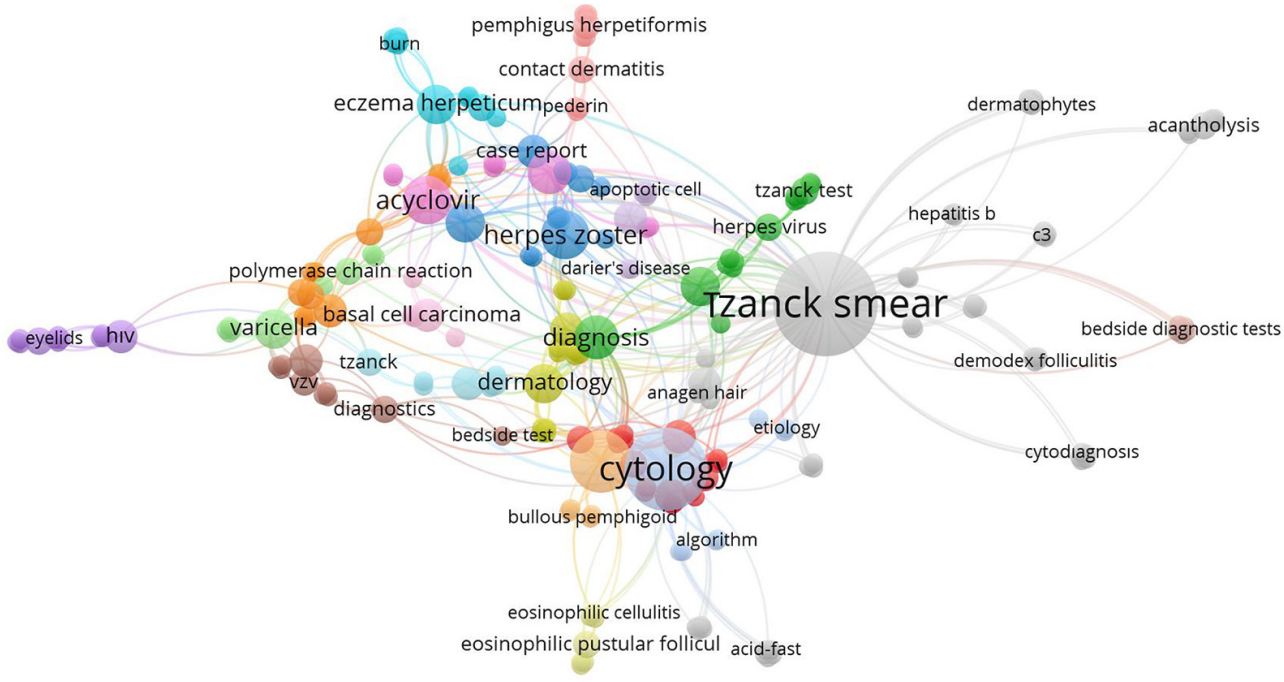

Figure 8.1. Shows how keywords are used together in the same publications. The size of each keyword reflects frequency, while link strength reflects co-occurrence. "Tzanck smear", "cytology", and "pemphigus" form central clusters

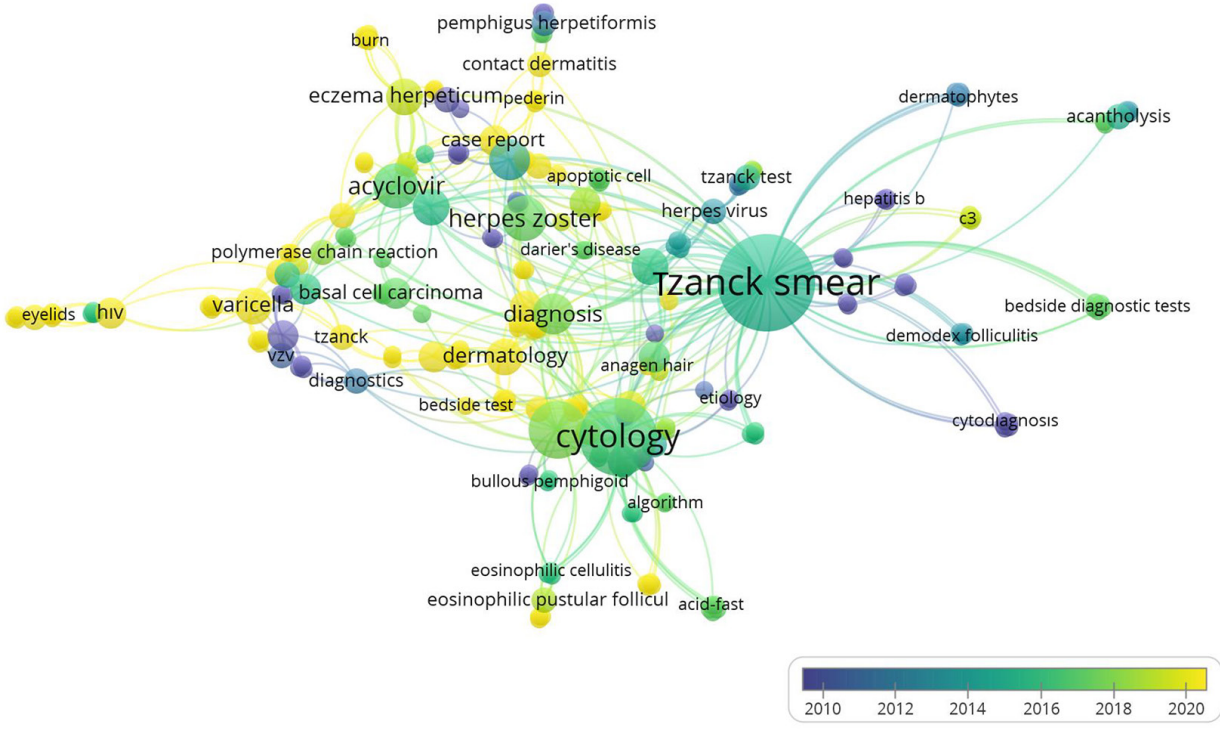

Figure 8.2. Similar to Figure 9 but color-coded by average publication year, helping identify shifts in topic focus over time

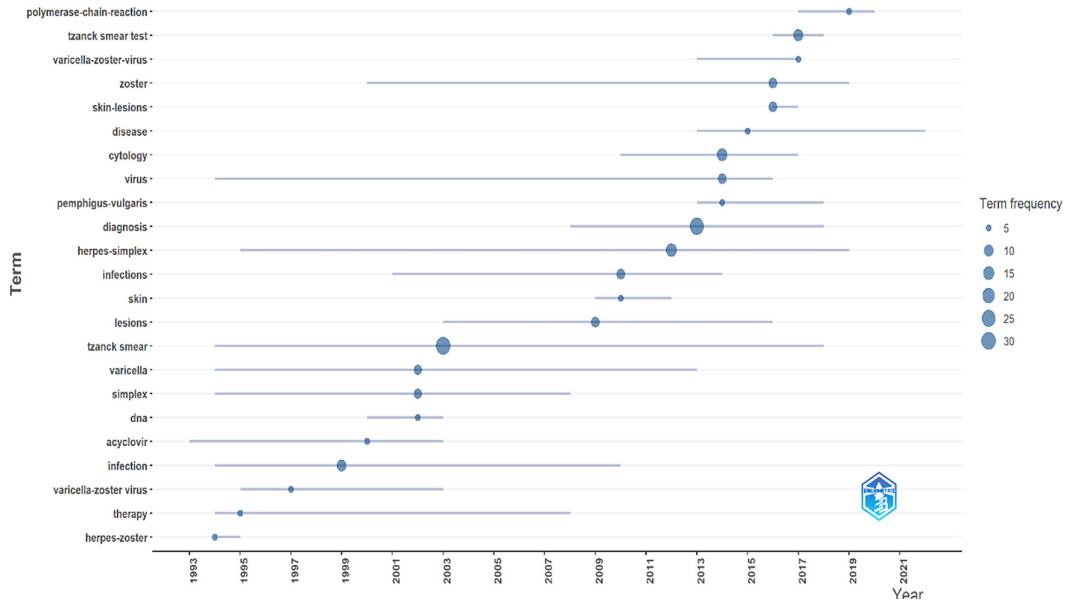

Figure 9. Line graph showing the changing usage rates of top keywords over the years. Helps visualize rising or declining interest in subtopics such as "acyclovir", "herpes zoster", and "skin tumors"

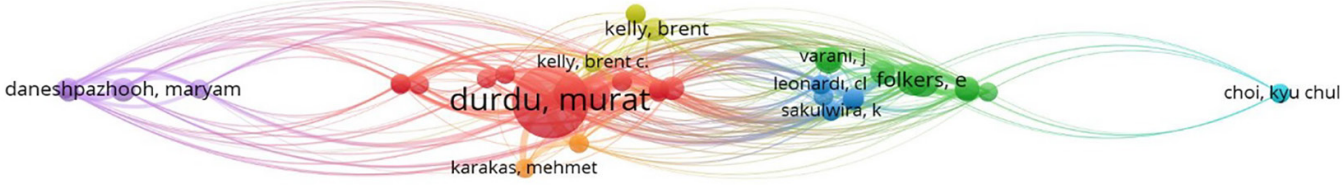

Figure 10. Visual representation of authors who cite the same references. Strong coupling indicates thematic or methodological similarity. Durdu M. again emerges as a central person with the highest coupling strength

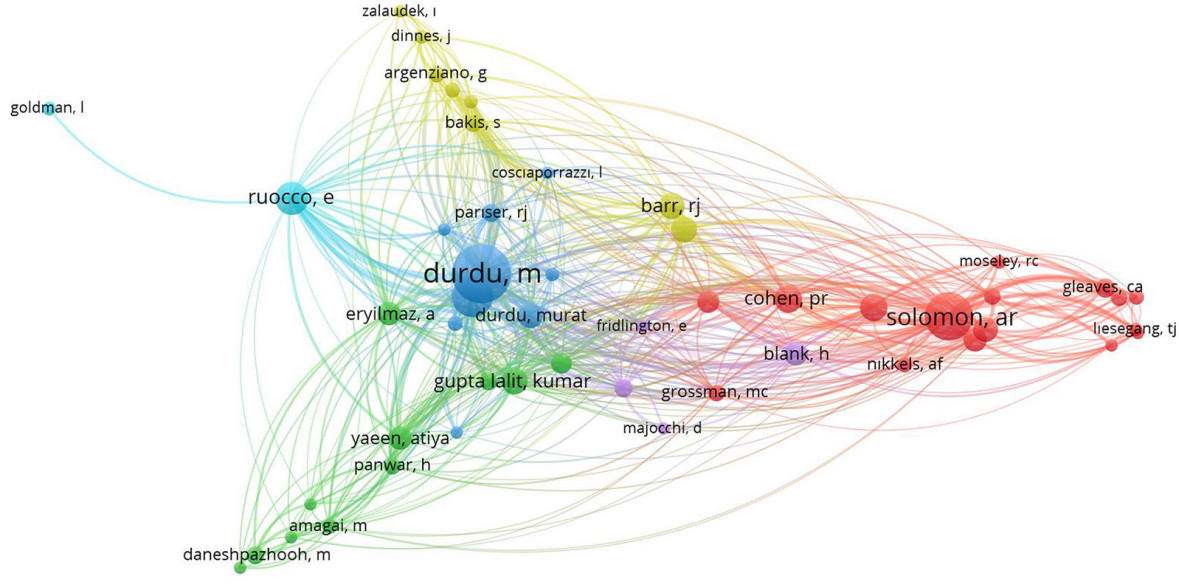

Figure 11. Authors that are frequently cited together by other articles form this network. Clusters reflect groups of authors perceived as conceptually linked. High co-citation implies foundational or frequently referenced work

Discussion

Bibliometrics is a scientific field that provides statistical analysis of academic literature, defining publication and citation trends in a specific area.[4] In this study, an attempt was made to create quantitative maps of studies conducted on the topic of Tzanck smear. This analysis provides a comprehensive overview of the Tzanck smear topic between 1983 and 2023, offering significant insights into global trends, productive authors and countries, leading journals, and influential publications.

The Tzanck smear has been studied in dermatology for various conditions, including vesiculobullous diseases (e.g., pemphigus group diseases, Stevens-Johnson syndrome/toxic epidermal necrolysis, staphylococcal scalded skin syndrome), infectious diseases (e.g., impetigo, fungal infections primarily dermatophytes; and candidal infections, herpes group diseases, viral diseases like molluscum contagiosum, cutaneous leishmaniasis), genodermatoses (e.g., Hailey-Hailey disease, Darier disease), and cutaneous tumors (e.g., basal cell carcinoma, squamous cell carcinoma, Paget's disease, Langerhans cell histiocytosis).[16] The herpes virus group and pemphigus have long been central topics in Tzanck smear research and continue to be prominent today. In recent years, there has been a notable rise in publications related to the Monkeypox virus.[17,18] A review of recent literature suggests that the Tzanck smear is gaining broader application in specific areas of dermatology, particularly in cutaneous malignancies and granulomatous diseases, and its use is expected to increase in these fields.

According to bibliometric data, the leading authors by publication count are Durdu M, Seckin D, and Folkers E, while the leading authors by citation count are Durdu M, Leonardi CL, and Nahass GT. Identifying prominent authors by publication and citation count can help researchers prioritize relevant publications during literature reviews.

The leading countries publishing on Tzanck smear are the USA, India, and Türkiye. Encouraging more contributions from countries currently underrepresented in this field could enhance both the literature and the global understanding of the topic. Collaboration analyses between countries and authors highlight the importance of multicenter studies for comprehensive global assessments.

Co-authorship analysis reveals that several authors have consistently collaborated over time. Among them, Folkers E and Durdu M (each with a total link strength of 16), and Oranje AP (link strength of 13) stand out as key figures in collaborative networks.

Türkiye's prominent role in authorship and citation metrics suggests a strong research base that can be leveraged for future multicenter collaborations. These insights can guide researchers in selecting relevant topics, target journals, and potential collaborators. In this study, Türkiye ranked third globally in the number of publications on Tzanck smear, following the USA and India. Among the top 10 most productive authors, multiple contributors are affiliated with Turkish institutions, including Durdu M, who is the most prolific and most cited author. This demonstrates that Türkiye has become a central node in Tzanck smear research, especially in terms of clinical application and academic output. Increasing inter-institutional collaboration within Türkiye and promoting multicenter bibliometric studies could further enhance this contribution.

According to the annual distribution of publications on Tzanck smear, the first publications on this topic appeared in 1983, and contributions have been consistently made to the literature almost every year since then, albeit with fluctuations, up to 2024. The three peaks, particularly in 2009, 2017, and 2022, indicate a greater inclination towards publishing on the subject and a higher number of publications in those years.

Looking at the journals where Tzanck smear topics are most frequently published and cited, these include the Journal of the American Academy of Dermatology, International Journal of Dermatology, Indian Journal of Dermatology, Venereology and Leprosy, JAMA, and Archives of Dermatology. From this, it appears that studies on Tzanck smears attract the attention of prestigious journals. Furthermore, identifying these articles will assist researchers both in pre-publication literature searches and in selecting suitable journals for their manuscripts. Among the most frequently used keywords in Tzanck smear publications are "Tzanck smear", "cytology", "pemphigus", "acyclovir", and "herpes zoster". Link strength analysis indicates that these terms are often used together in the same articles. Topics related to herpes and varicella viruses have remained consistently prominent over the years, whereas monkeypox-related keywords have emerged more recently. Keywords play a critical role in summarizing a study's content and enhancing its visibility in databases. Therefore, selecting keywords that are MeSH-compliant, relevant, up-to-date, and semantically linked is essential during the study design phase.

Study Limitations

One of the significant limitations of the study is that the analyses were confined to publications indexed in the Web of Science Core Collection, excluding research from other databases such as Scopus, PubMed, and Google Scholar. Therefore, some important studies, particularly those with limited international visibility, may have been overlooked.

To make a comparison between these databases via PubMed, we observed that the overall trends compared with the PubMed database were parallel to those found in Web of Science. However, because the software used in the data analysis process (VOSviewer, Biblioshiny) did not integrate with PubMed data, the visualizations were based solely on Web of Science data.

Another limitation is the reliance on citation counts as a measure of impact. While citations provide a useful insight into a publication's impact, they may not fully reflect the quality or significance of the research. Some highly cited studies may be outdated or criticized for methodological flaws, yet continue to receive citations. Conversely, newer studies may not have accumulated enough citations to be recognized in bibliometric analyses. Therefore, more comprehensive studies on this topic are needed.

Conclusion

This study fills an important gap in the literature by representing the first comprehensive bibliometric analysis specifically focused on the topic of Tzanck smear. In the literature, researchers, countries, and journals have shown varying trends regarding Tzanck smear over the years. Türkiye's prominent role in authorship and citation metrics suggests a strong research base that can be leveraged for future multicenter collaborations. The statistical evaluation of these trends bibliometrically can provide a roadmap for researchers planning to work on this topic when designing their studies.

Ethics

Ethics Committee Approval: Not applicable.

Informed Consent: Not applicable.

Footnotes

Authorship Contributions

Concept: E.A., S.A.T., İ.Ö., M.D., R.D., Design: E.A., S.A.T., İ.Ö., M.D., R.D., Data Collection or Processing: E.A., Analysis or Interpretation: E.A., S.A.T., İ.Ö., M.D., R.D., Literature Search: E.A., Writing: E.A., S.A.T.

Conflict of Interest: The authors declared that they have no conflict of interest.

Financial Disclosure: The authors declared that this studyreceived no financial support.

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Original Article

The Relationship Between Depression Levels and Suicide Risk in Pediatric Patients with Alopecia Areata and the Oxidant-Antioxidant Balance

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Abstract

Aim: This research aimed to investigate oxidative stress (OS) markers and their relation to depressive symptoms and suicide tendencies in children diagnosed with alopecia areata (AA) compared to a healthy cohort.

Materials and Methods: A cross-sectional design was implemented, enrolling 30 children with AA and 30 healthy peers. The biomarkers evaluated included malondialdehyde (MDA), superoxide dismutase (SOD), total antioxidant status (TAS), total oxidant status (TOS), OS index (OSI), asymmetric dimethylarginine (ADMA), and homocysteine. Receiver operating characteristic curve analysis was used to determine their diagnostic potential. Psychiatric conditions were assessed using Diagnostic and Statistical Manual of Mental Disorders, fifth edition based interviews, while depressive severity and suicide risk were measured through the Beck Depression Inventory and the Suicide Probability Scale, respectively.

Results: Children with AA displayed significantly elevated levels of MDA, TOS, OSI, ADMA, and homocysteine, while TAS and SOD values were notably reduced ($P < 0.001$). Depression and suicide scores did not differ significantly between groups. Diagnostic accuracy for TAS, TOS, OSI, and SOD reached 96.7% sensitivity and 93.3% specificity. Homocysteine, MDA, and ADMA also showed acceptable predictive power.

Conclusion: The findings support a possible etiological contribution of OS in the development of AA.

Keywords: Child psychiatry, alopecia areata, oxidative stress, depression, suicide

Introduction

Alopecia areata (AA) is a relatively common, non-scarring, immune-mediated disorder that causes abrupt hair loss in well-defined patches. It affects individuals across all age groups, demographics, and impacts roughly 2% of the population.[1] Hair loss can remain localized or progress to involve the entire scalp (alopecia totalis) or the whole body (alopecia universalis).[2]

Despite extensive research, the exact pathogenesis of AA remains elusive. However, current evidence points toward an interplay of hereditary factors, immune system dysfunction, psychological triggers, and environmental influences.[3-5] Many AA patients also experience psychiatric disturbances, particularly anxiety and depression.[6] A subset of patients has been identified as being even at increased risk for suicidal thoughts or behaviors, with one study reporting this in nearly 13% of individuals with AA.[7]

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The skin acts as a vital barrier against environmental aggressors and is continuously exposed to oxidative elements. Such prooxidant exposure promotes excessive production of reactive oxygen species (ROS), which are known to interfere with cellular signaling and proliferation, as well as modulate apoptotic mechanisms. These disruptions in programmed cell death have been implicated in various dermatological disorders.[8,9] Oxidative stress (OS) arises from a disruption in the balance between the generation of ROS and the body's antioxidant defenses. Elevated ROS levels or insufficient antioxidant protection can trigger cellular injury and inflammation, mechanisms suspected to be involved in AA. OS emerges when endogenous antioxidant defenses fail to neutralize an overabundance of oxidants, creating a redox imbalance. This imbalance has been associated with the pathophysiology of AA.[10-12] Although the underlying mechanisms of AA remain partly unknown, the condition is widely regarded as autoimmune in origin. OS is believed to contribute to autoimmune processes by promoting inflammatory responses and impairing immune regulation through apoptotic induction.[13]

OS is also implicated in psychiatric conditions, but whether it is a cause or a consequence of such disorders remains unclear.[14]

This study was designed to assess and compare the OS parameters, depression severity, and suicide probability between AA patients and healthy controls; and to explore potential correlations among them.

Materials and Methods

Study Groups

The sample size for the study was calculated with the GPower 3.1 program. The required sample size for this study was determined using an a priori power analysis based on a two-tailed Wilcoxon-Mann-Whitney test comparing two groups' distributions. The effect size was derived from the study by Yıldız Miniksar and Göçmen[15] in which the mean and standard deviation (SD) of malondialdehyde (MDA) levels were reported as 0.29±0.003 in the major depressive disorder (MDD) group and 0.33±0.04 in the control group. Based on these values, the calculated effect size was d = 1.13. Using this effect size, with a significance level of $\alpha = 0.05$ and statistical power of $1-\beta = 0.95$, the power analysis indicated that 23 participants per group, or 46 in total, would be required.

This research used a cross-sectional methodology and included a total of 60 individuals: 30 adolescents aged between 12 and 18 years diagnosed with AA and 30 age-matched healthy controls. Participants in the AA group were recruited from the Department of Dermatology, Yozgat Bozok University Medical Faculty over a five-month period from January to May 2021. Inclusion criteria were based on clinical diagnosis, and participants were excluded if they had chronic systemic conditions, cognitive impairments, were undergoing psychiatric or systemic treatment, or had other visible dermatological disorders unrelated to AA.

Disease severity in the AA group was assessed using the Severity of Alopecia Tool (SALT), categorizing individuals into mild (< 50% scalp involvement, S1-S2) and severe (≥ 50% involvement, S3-S5) groups. All dermatological assessments were conducted by a single experienced dermatologist to ensure consistency.[16] Subsequently, participants from both groups underwent psychiatric evaluation by a certified child and adolescent psychiatrist. A structured clinical interview based on the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, was used to diagnose any co-existing psychiatric conditions.[17] Depression levels were determined through the Beck Depression Inventory (BDI), while suicide risk was assessed using the Suicide Probability Scale (SPS). This study was approved by the Clinical Research Ethics Committee of Yozgat Bozok University (approval number: 2017-KAEK-189, date: 16.12.2020). Written informed consent was obtained from all participants.

Biochemical Analysis

Following an overnight fast of 12 hours, 3 to 5 mL of venous blood was collected from each participant. The blood samples were transferred to biochemistry tubes and centrifuged at 4000 rpm for ten minutes to separate the serum. These serum samples were stored at -80 °C until they were analyzed.

Serum total antioxidant status (TAS) and total oxidant status (TOS) were measured using Erel's commercial kits (Rel Assay Diagnostics, Mega Tip, Gaziantep, Türkiye). The OS index (OSI) was computed by dividing TOS by TAS and expressed in arbitrary units as OSI = TOS (μmol H_2O_2/L)/TAS (mmol Trolox equivalent/L).

TAS was measured via a method based on the suppression of the 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonate) radical cation. TOS was determined through the oxidation of a ferrous ion-o-dianisidine complex to ferric ion, which forms a colored compound with xylene orange in acidic medium. The intensity of the color, measured spectrophotometrically, correlated with the amount of oxidant in the serum. All readings were calibrated using hydrogen peroxide as a reference standard.

Superoxide dismutase (SOD) activity was quantified using a SOD assay kit (Rel Assay Diagnostics, Mega Tip, Türkiye), while MDA concentrations were determined via a colorimetric kit from Cayman Chemical (Michigan, United States of

America). Levels of asymmetric dimethylarginine (ADMA) and homocysteine were evaluated using commercial ELISA kits provided by Elabscience (Wuhan, China). All laboratory analyses were performed in the same lab using a BioTek EL × 800 microplate reader, following the protocols and wavelengths specified by the respective kit manufacturers.

Psychological Measurement Tools

Beck Depression Inventory (BDI): Originally developed by Beck et al.[18] this 21-item self-assessment scale uses a 4-point Likert format to quantify depressive symptoms. Score categories are as follows: 0-9 (minimal), 10-16 (mild), 17-29 (moderate), and 30-63 (severe). The Turkish validation was carried out by Hisli.[19]

Suicide Probability Scale (SPS): The SPS comprises 36 self-report items across four domains-hopelessness, suicidal ideation, negative self-image, and hostility.[20] Responses are rated from 1 (never/rarely) to 4 (almost/always). Higher total scores reflect increased suicide risk. The Turkish adaptation was validated by Atlı et al.[21]

Statistical Analysis

All statistical analyses were performed using an appropriate software package. Descriptive statistics were presented in tabular form. The independent samples t-test was used to compare means between groups, while non-parametric tests were applied where assumptions of normality were not met. The chi-square test assessed categorical data. Pearson correlation was employed to explore relationships between variables such as age, disease duration, and severity, OS markers, depression scores, and suicide risk. Receiver operating characteristic (ROC) analysis was used to determine the sensitivity and specificity of biochemical markers in predicting AA. A P value < 0.05 was accepted as statistically significant.

Results

This study included 60 participants: 30 individuals diagnosed with AA and 30 healthy controls. Among those with AA, 53.3% were female, with a mean age of 14.9 years (SD: 1.77), whereas the control group had a slightly higher proportion of females (66.7%) and a mean age of 16.0 years (SD: 1.70), yielding a statistically significant age difference (P = 0.017). In terms of disease characteristics, over half of the AA group (53.3%, n = 16) reported a disease duration of less than 6 months. A smaller portion (26.7%, n = 8) had lived with the condition for over one year. The majority (80%) presented with a mild severity level, based on SALT scores categorized as S1 or S2 (Table 1).

Oxidative Stress Biomarkers

Evaluation of OS-related biomarkers revealed that patients in the AA group exhibited higher mean values of MDA, TOS, OSI, ADMA, and homocysteine, compared to their healthy counterparts. Conversely, levels of SOD and TAS were significantly reduced in the AA group. All of these differences were statistically significant (P < 0.001), supporting increased oxidative imbalance in the patient group (Table 1, Figure 1).

Psychiatric Evaluation

From a psychiatric standpoint, four children in the AA group met criteria for MDD, while three were diagnosed with generalized anxiety disorder. In comparison, two individuals in the control group were found to have major depression. However, the prevalence of psychiatric comorbidities did not differ significantly between the two groups. The average BDI scores also showed no significant difference between AA patients and controls. Additionally, no group differences were observed in the distribution of depression severity categories (minimal, mild, moderate, or severe). Regarding suicide risk, the mean SPS score was higher in the control group (67.6%) than in the AA group (60.4%), but the difference did not reach statistical significance (P = 0.079). Subscale analysis of the SPS showed that the control group scored significantly higher in hopelessness and hostility domains (P < 0.05), whereas no significant variation was detected in the suicide ideation and negative self-evaluation subscales (Table 1).

ROC Curve Analysis

ROC analysis demonstrated that the OS indicators SOD, TAS, TOS, and OSI had high diagnostic value in differentiating AA patients from controls, each with 96.7% sensitivity and 93.3% specificity. Similarly, homocysteine (96.7% sensitivity; 83.3% specificity), MDA (93.3%; 83.3%), and ADMA (73.3%; 70.0%) also showed acceptable predictive power, although ADMA had the lowest discriminatory capability among the markers analyzed (Table 2, Figure 2).

Correlation Findings

In the AA group, a moderately strong positive correlation (r = 0.667) was identified between disease duration and disease severity. However, no statistically significant relationship was found between disease duration or severity and OS biomarkers, except for ADMA. Notably, weak positive correlations were observed between disease duration and the following variables: ADMA (r = 0.368), BDI scores (r = 0.368), suicide ideation (r = 0.408), and hostility (r = 0.436). In both AA and control groups, age was moderately associated with higher BDI scores: AA group (r = 0.420), control group

Table 1. Mean of oxidative stress parameters and BDI and SPS scores in alopecia areata and control groups

		Groups				*t*	*P*
		Control (n = 30)		Alopecia areata (n = 30)			
		Mean	SD	Mean	SD		
Gender	Male (n,%)	10	33.3	14	46.7	1.111[a]	0.292
	Female (n,%)	20	66.7	16	53.3		
	Age (year)	16.0	1.70	14.9	1.77	2.455	**0.017**
Alopecia areata duration	0-6 months			16	53.3		
	7-12 months			6	20.0		
	≥ 13 months			8	26.7		
SALT score	S1-S2			24	80.0		
	S3-S5			6	20.0		
	MDA (µmol/L)	0.70	0.09	0.88	0.06	8.842	**< 0.001**
	SOD (U/mL)	19.06	1.19	15.99	1.15	10.185	**< 0.001**
	TAS (µmol Trolox Eq/L)	0.86	0.04	0.73	0.04	13.070	**< 0.001**
OPS	TOS (µmol H_2O_2 Eq/L)	10.90	0.71	13.08	0.94	10.120	**< 0.001**
	OSI (arbitrary unit)	1.27	0.14	1.80	0.23	10.963	**< 0.001**
	ADMA (µmol/L)	0.80	0.07	0.91	0.10	4.667	**< 0.001**
	Homocysteine (mcmol/L)	3.94	0.21	4.54	0.30	9.075	**< 0.001**
	BDI scores	12.00	8.55	11.03	9.65	0.411	**0.683**
	Minimal (0-9) (n,%)	15	50.0	17	56.7	0.258[b]	**1.000**
	Mild (10-16) (n,%)	5	16.7	4	13.3		
	Moderate (17-29) (n,%)	9	30.0	7	23.3		
	Severe (30-63) (n,%)	1	3.3	2	6.7		
	SPS total	67.60	15.40	60.40	15.81	1.786	0.079
	Hopelessness	25.43	6.38	21.60	6.04	2.390	**0.020**
	Suicide ideation	11.90	2.95	10.47	3.88	1.612	0.112
	Negative self-evaluation	17.97	5.54	18.23	5.00	0.196	0.845
	Hostility	12.30	3.50	10.10	4.12	2.230	**0.030**
	Total	30	100.0	30	1.00		

[a]Chi-square test, [b]Kolmogorov-Smirnov test, SALT: Severity of Alopecia Tool, BDI: Beck Depression Inventory, SPS: Suicide Probability Scale, OPS: Oxidative stress parameters, MDA: Malondialdehyde, SOD: Superoxide dismutase, TAS: Total antioxidant status, TOS: Total oxidant status, OSI Index: Oxygen saturation index, ADMA: Asymmetric dimethyl arginine, SD: Standard deviation

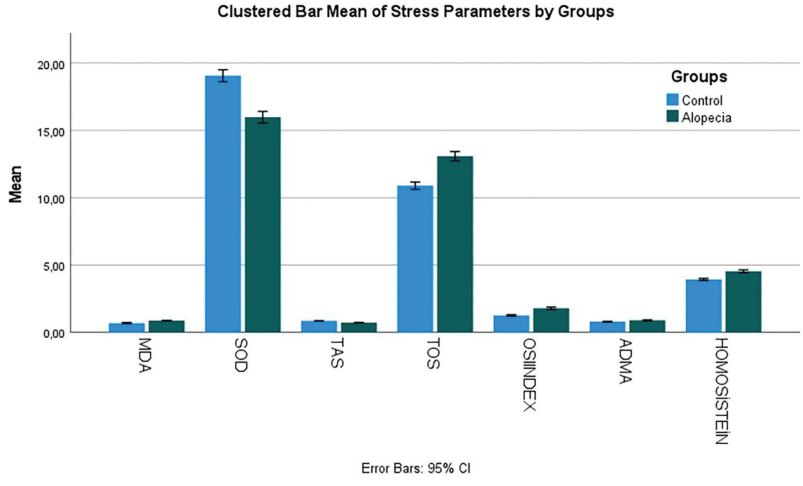

Figure 1. Mean oxidative stress parameters in alopecia areata and control groups
MDA: Malondialdehyde, SOD: Superoxide dismutase, TAS: Total antioxidant status, TOS: Total oxidant status, OSI index: Oxygen saturation index, ADMA: Asymmetric dimethyl arginine

(r = 0.478) (Table 3). ANCOVA ruled out a significant association between disease duration and BDI score (P = 0.472); rather, it identified participant age as a significant predictor of depressive symptoms ($P < 0.001$).

In the control group, no significant links were found between oxidative markers and either psychiatric status or age. As expected, moderate correlations were identified between depression severity and suicide risk, along with significant associations between SPS subscales across both groups (Tables 3, 4).

Discussion

The present study set out to examine OS markers in relation to psychological outcomes-specifically depression and suicide risk-in pediatric patients with AA, compared to a healthy control group. Our results show a distinct biochemical profile in AA patients, with significantly increased levels of MDA, TOS, OSI, ADMA, and homocysteine, and markedly reduced levels of TAS and SOD, consistent with previous findings linking oxidative imbalance to AA pathophysiology.

Numerous studies have investigated redox disturbances in AA, with many reporting heightened levels of lipid peroxidation products and diminished activity of antioxidant enzymes in affected individuals compared to healthy controls.[22] Our study corroborates these findings, showing significantly elevated MDA, TOS, OSI, ADMA, and homocysteine in AA patients, alongside reduced TAS and SOD activity. These observations suggest a tilt in the oxidative-antioxidative balance toward a prooxidant state. For instance, MDA, a terminal product of lipid peroxidation, has been shown to accumulate both in plasma and scalp tissues in AA patients.[23] Furthermore, reductions in SOD activity have been noted in previous research, with evidence linking declining SOD levels to increasing disease severity.[24,25] A systematic review and meta-analysis by Acharya and Mathur[24] highlighted similar trends: namely, increases in oxidative indicators like MDA, nitric oxide, and TOS, and decreases in antioxidants such as SOD, paraoxonase, glutathione peroxidase, and TAS. This study also found a connection between oxidative levels and the extent of hair loss in AA. However, our own analysis did not identify a statistically significant relationship between OS

Table 2. Sensitivity and specificity of oxidative stress parameters in alopecia areata based on ROC curve analysis

Test result variable (s)	Area	Sig.	Cut-off point	Sensitivity %	Specificity %
MDA	0.932	0.000	< 0.785	93.3	83.3
SOD	0.022	0.000	> 17.705	96.7	93.3
TAS	0.007	0.000	> 0.795	96.7	93.3
TOS	0.979	0.000	< 11.93	96.7	93.3
OSI	0.986	0.000	< 1.485	96.7	93.3
ADMA	0.804	0.000	< 0.855	73.3	70.0
Homocysteine	0.971	0.000	< 4.170	96.7	83.3

MDA: Malondialdehyde, SOD: Superoxide dismutase, TAS: Total antioxidant status, TOS: Total oxidant status, OSI index: Oxygen saturation index, ADMA: Asymmetric dimethyl arginine, ROC: Receiver operating characteristic

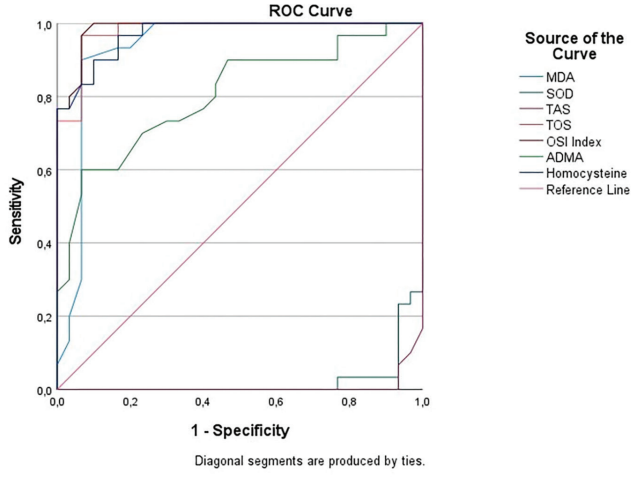

Figure 2. Discriminatory power of oxidative stress markers for alopecia areata using ROC analysis
ROC: Receiver operating characteristic, MDA: Malondialdehyde, SOD: Superoxide dismutase, TAS: Total antioxidant status, TOS: Total oxidant status, OSI index: Oxidative stress index, ADMA: Asymmetric dimethylarginine

Table 3. Correlation between oxidative stress parameters and disease duration and BDI score and SPS score in the alopecia areata group

	Disease duration	SALT score	Age	MDA	SOD	TAS	TOS	OSI	ADMA	Homo-cysteine	BDI score	SPS total	Hope-lessness	Suicide ideation	Negative self-evaluation
Alopecia severity	0.657**	1													
Age (year)	-0.187	0.030	1												
MDA	-0.175	0.047	0.203	1											
SOD	-0.171	-0.224	-0.079	-0.664**	1										
TAS	-0.118	-0.185	-0.105	-0.683**	0.962**	1									
TOS	0.183	.0225	0.111	0.684**	-0.989**	-0.928**	1								
OSI	0.207	0.226	0.149	0.698**	-0.967**	-0.926**	0.980**	1							
ADMA	**0.396***	0.277	0.080	0.317	-0.844**	-0.794**	0.847**	0.891**	1						
Homocysteine	0.242	0.246	0.144	0.628**	-0.965**	-0.913**	0.980**	0.994**	0.920**	1					
BDI score	**0.368***	0.260	**0.420***	-0.199	0.093	0.068	-0.092	-0.071	0.032	-0.057	1				
SPS score total	0.296	0.058	0.243	-0.250	0.060	0.030	-0.059	-0.023	0.135	0.001	**0.739****	1			
Hopelessness	0.079	-0.092	0.296	-0.172	0.041	-0.014	-0.046	0.001	0.123	0.013	**0.617****	0.894**	1		
Suicide ideation	**0.408***	0.141	0.183	-0.217	0.080	0.016	-0.093	-0.047	0.101	-0.030	**0.721****	0.849**	0.719**	1	
Negative self-evaluation	0.165	-0.004	0.190	-0.192	0.078	0.012	-0.091	-0.079	0.008	-0.064	**0.600****	0.811**	0.615**	0.585**	1
Hostility	**0.436***	0.229	0.096	-0.270	-0.001	0.104	0.040	0.050	0.232	0.089	**0.528****	0.745**	0.543**	0.554**	0.447*

*Correlation is significant at the 0.05 level (2-tailed)
**Correlation is significant at the 0.01 level (2-tailed)
MDA: Malondialdehyde, SOD: Superoxide dismutase, TAS: Total antioxidant status, TOS: Total oxidant status, OSI index: Oxygen saturation index, ADMA: Asymmetric, BDI: Beck Depression Inventory, SPS: Suicide Probability Scale

Table 4. Correlation between oxidative stress parameters and BDI score and SPS score in the control group

	Age	MDA	SOD	TAS	TOS	OSI	ADMA	Homo-cysteine	BDI Score	SPS Total	Hope-lessness	Suicide ideation	Negative self-evaluation
MDA	0.072	1											
SOD	-0.040	-0.575**	1										
TAS	-0.181	-0.631**	0.932**	1									
TOS	0.096	0.430*	-0.827**	-0.809**	1								
OSI	0.161	0.536**	-0.831**	-.0894**	0.868**	1							
ADMA	0.250	-0.455*	-0.303	-0.292	0.367*	0.339	1						
Homocysteine	0.157	0.211	-0.768**	-0.773**	0.882**	0.804**	0.591**	1					
BDI score	**0.478****	0.239	-0.213	-0.251	0.008	0.053	0.017	0.067	1				
SPS total	**0.505****	0.000	0.041	-0.049	-0.125	-0.054	-0.043	-0.083	**0.743****	1			
Hopelessness	**0.441***	0.145	0.084	-0.011	-0.192	-0.122	-0.281	-0.198	**0.650****	0.924**	1		
Suicide ideation	0.151	-0.055	-0.173	-0.219	0.109	0.174	0.101	0.243	**0.523****	0.662**	0.511**	1	
Negative self-evaluation	**0.542****	-0.083	0.054	-0.037	-0.104	-0.008	0.118	-0.050	**0.649****	0.889**	0.763**	0.462*	1
Hostility	**0.435***	-0.088	0.086	0.047	-0.129	-0.150	0.054	-0.130	**0.618****	0.754**	0.605**	0.407*	0.551**

*Correlation is significant at the 0.05 level (2-tailed)
**Correlation is significant at the 0.01 level (2-tailed)
MDA: Malondialdehyde, SOD: Superoxide dismutase, TAS: Total antioxidant status, TOS: Total oxidant status, OSI index: Oxygen saturation index, ADMA: Asymmetric dimethyl arginine, BDI: Beck Depression Inventory, SPS: Suicide Probability Scale

parameters and AA severity. Mild cases accounted for 80% of AA patients. The significantly lower number of severe AA cases may explain the lack of a significant difference between disease severity and OS.

Hair loss in pediatric AA patients often causes distress, contributing to reduced self-image and emotional well-being. These psychosocial factors may predispose individuals to anxiety or depressive disorders.[6] Conversely, chronic psychological stress has been suggested as a potential initiating factor for AA, indicating a possible bidirectional relationship.[26] In our study, although psychiatric diagnoses were more frequent in the AA group, the difference was not statistically significant. Similarly, BDI scores and depression severity classifications did not differ meaningfully between the AA and control groups. While the control group had a higher mean SPS score, along with greater hopelessness and hostility subscale scores, these differences lacked statistical significance. Notably, the control group was older and included a higher proportion of females-both factors previously linked to elevated suicide risk during adolescence.[26] Literature suggests that suicidal behavior becomes more prevalent with increasing age and is more common in girls.[27] These demographic differences, along with the fact that 80% of AA cases in our sample were mild, may explain the similar psychiatric outcomes across groups.

Given the dual role of OS and psychological stress in AA etiology, we further assessed whether psychiatric conditions were associated with oxidative changes in AA patients.[6,25] Previous research has implicated OS in psychiatric illnesses, particularly mood and anxiety disorders.[28,29] A systematic review of 10 studies also found that AA has significant psychosocial effects on pediatric and adolescent populations, with deterioration in quality of life, increased anxiety levels, and higher rates of depression.[30] A meta-analysis examining both adult and pediatric AA patients found that depression and anxiety were significantly higher in adult patients than in children. This suggests that appearance and body image may be more important in adolescents and adults than in childhood.[31] However, our results showed no significant relationship between OS biomarkers and psychiatric measures, including BDI and SPS scores. A recent case-control study by Cakirca et al.[32] also explored this topic and, despite finding elevated TOS and TAS values alongside higher anxiety and depression scores in AA patients, reported no direct correlation between oxidative markers and psychological symptoms.

While a subset of studies supports the idea that mental health disorders are more prevalent in AA populations, others emphasize the role of psychological stress in the initial onset and worsening of AA.[5,6,33] In our case, the limited sample size and predominance of mild AA could have weakened these associations. Importantly, OS is not only implicated in disease pathogenesis but may also serve as a therapeutic target. Antioxidant agents, particularly in mild to moderate cases, may offer a complementary approach to standard treatments.

In our ROC analysis, OS markers such as SOD, TAS, TOS, and OSI demonstrated high sensitivity (96.7%) and specificity (93.3%) in distinguishing AA patients from healthy controls. Other markers, including homocysteine (96.7% sensitivity, 83.3% specificity), MDA (93.3%, 83.3%), and ADMA (73.3%, 70.0%), also showed diagnostic potential, though to varying degrees. These results reinforce the utility of redox biomarkers in understanding the disease and potentially tracking its course.

Study Limitations

Despite its contributions, this study has certain limitations. The sample size was relatively modest, and group imbalances in age and gender could have influenced both clinical and psychological outcomes. Additionally, the predominance of mild AA cases may have limited our ability to detect associations with disease severity.

Conclusion

The present findings reinforce the involvement of OS in the development of AA. Although psychiatric parameters did not differ significantly between groups, the clear oxidative imbalance in AA patients suggests a biochemical role in the disease's underlying mechanisms. Antioxidant-based interventions may provide a valuable adjunct to standard therapy, especially in less severe cases. Further studies involving larger, more diverse samples are warranted to better understand these relationships and to evaluate antioxidant treatments more comprehensively.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of Yozgat Bozok University (approval number: 2017-KAEK-189, date: 16.12.2020).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.Y.M., E.Ç., Concept: D.Y.M., E.Ç., Design: D.Y.M., E.Ç., Data Collection or Processing: D.Y.M., E.Ç., Analysis or Interpretation: A.Y.G., M.K., Literature Search: D.Y.M., E.Ç., A.Y.G., Writing: D.Y.M., E.Ç., M.K.

Conflict of Interest: The authors declared that they have no conflict of interest.

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Case Report

A Unique Overlap of Scarring and Non-Scarring Alopecia in Primary Cutis Verticis Gyrata

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Abstract

Cutis verticis gyrata (CVG) is a rare scalp disorder characterized by cerebriform thickening and folding of the scalp skin. It can present as a primary essential form without underlying systemic involvement. Alopecia, classified as scarring or nonscarring, may rarely accompany CVG. We report a 55-year-old female with primary essential CVG exhibiting both nonscarring alopecia areata and scarring lichen planopilaris, which were confirmed histopathologically. No neurological, ophthalmological, or systemic abnormalities were present. Magnetic resonance imaging revealed no intracranial or cranial bone pathology. To our knowledge, this is the first reported case of simultaneous scarring and non-scarring alopecia in a patient with primary essential CVG. This rare coexistence may reflect the presence of multiple autoimmune pathways targeting different segments of the hair follicle. Clinicians should consider combined pathological mechanisms in unusual alopecia presentations associated with CVG.

Keywords: Cutis verticis gyrata, alopecia areata, lichen planopilaris, scarring alopecia, autoimmune overlap

Introduction

Cutis verticis gyrata (CVG) is a rare dermatological condition characterized by excessive thickening and folding of the scalp skin, resulting in a cerebriform appearance that mimics the surface of the brain. CVG is classified into three subtypes: primary essential, primary non-essential (associated with neuropsychiatric or ophthalmological disorders), and secondary (due to local or systemic causes such as tumors, inflammatory dermatoses, or trauma).[1] The pathogenesis of primary CVG remains poorly understood. Proposed mechanisms include hormonal imbalances, such as altered androgen metabolism, and abnormalities in connective tissue development. Histopathological findings in primary CVG are often non-specific, ranging from normal skin to hypertrophy of adnexal structures and increased dermal collagen. Alopecia is broadly divided into non-scarring and scarring types, depending on whether permanent destruction of hair follicles occurs. Alopecia areata (AA) is a common autoimmune form of non-scarring alopecia, whereas lichen planopilaris (LPP) represents a lymphocytic scarring alopecia.[2] To date, only a few cases have been reported in the literature that associate alopecia with CVG, and none have described the coexistence of both scarring and nonscarring types in the same patient with primary essential CVG. This report presents a unique case illustrating this rare overlap.

Case Report

A 55-year-old woman presented with progressive scalp deformity and hair loss. Ten years earlier, she had been diagnosed with seborrheic dermatitis and CVG based on scalp biopsy, but no follow-up was performed. On examination, alopecic patches and deep cerebriform folds were observed over the vertex and occipital scalp. Histopathology from these areas showed features of both scarring and non-scarring

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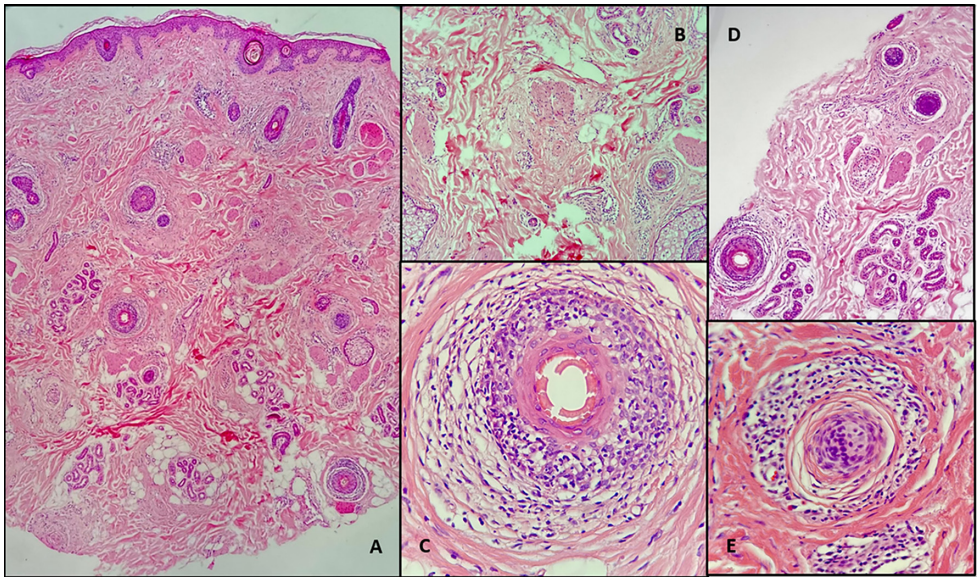

Figure 1. Histopathologic sections from scalp biopsies: (A) Follicular hypertrophy in dermis (H&E x 40). (B) Follicular scar tissue (H&E x 100). (C) Perifollicular lichenoid infiltrate at infundibular level, suggestive of LPP (H&E x 200). (D) Mixed pattern: LPP below, AA above in same field (H&E x 100). (E) Lymphocytic infiltration around anagen hair bulb (H&E x 200).
H&E: Hematoxylin and eosin, LPP: Lichen planopilaris, AA: Alopecia areata

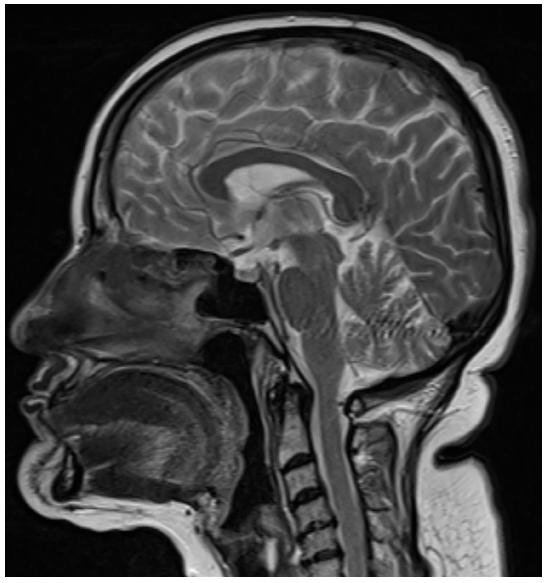

Figure 2. The clinical image of the patient's scalp shows the CVG pattern in the occipital region
CVG: Cutis verticis gyrata

alopecia: perifollicular lichenoid inflammation and fibrosis consistent with LPP, along with peribulbar lymphocytic infiltrates characteristic of alopecia areata (Figure 1). Systemic evaluation, including cranial magnetic resonance imaging, revealed no neurologic or ocular involvement or intracranial pathology (Figure 2). She was started on topical corticosteroids and scheduled for regular dermatologic follow-up. Written informed consent was obtained from the patient for publication.

Discussion

CVG is an uncommon condition involving hypertrophy of the scalp skin, forming undulating folds that resemble cerebral gyri. It may present as a primary essential form, with no systemic associations, or secondary to underlying local or systemic conditions.[1,3] Histopathology in primary CVG is often non-specific, though thickening of dermal collagen or adnexal hypertrophy may be observed. In our case, histologic features of CVG coexisted with findings diagnostic for both LPP (scarring alopecia) and AA (non-scarring alopecia).

Table 1. Cases of CVG with alopecia

Literature	Age	Gender	CVG type	Alopecia type
Buontempo et al.[7]	39	F	Primary essential	Primary scarring alopecia
Anansiripun and Suchonwanit[8]	24	M	Secondary	Scarring alopecia
Alonso Pereira et al.[9]	29	M	Secondary	Folliculitis decalvans, folliculitis keloidalis nuchae
Bonalumi Filho et al.[10]	43	F	Secondary	N/A
Alcántara González et al.[11]	48	M	Secondary	N/A
Yoo et al.[6]	28	M	Primary essential	Alopecia areata
Mishra et al.[12]	18	F	Primer essential	N/A
Saoji et al.[13]	48	M	Secondary	N/A
Pai and Rao[14]	25	M	Secondary	Scarring alopecia
Fox et al.[15]	Newborn	F	Congenital	N/A
van Geest et al.[16]	46	M	Secondary	N/A
Jeanfils et al.[17]	43	M	Secondary	N/A
Hamm and Argent[18]	41	F	Secondary	N/A
Yazici et al.[19]	7	F	Secondary	N/A
Kanwar et al.[20]	25	F	N/A	Tractional

N/A: No answer, F: Female, M: Male, CVG: Cutis verticis gyrata

Although both LPP and AA are considered autoimmune disorders, they typically exhibit distinct immunopathological profiles. The co-occurrence of scarring and non-scarring alopecia in the same patient raises the possibility of a shared underlying autoimmune predisposition, potentially targeting different components or layers of the hair follicle unit. This aligns with theories proposing that variable follicular immune privilege collapse may contribute to divergent clinical outcomes.[4,5] A literature review identified 15 prior cases of CVG with alopecia. Of these, one involved AA[6] and one primary CVG with scarring alopecia (Table 1).[7] However, to our knowledge, this is the first reported case of both forms of alopecia occurring simultaneously in a patient with primary essential CVG. Further studies are needed to clarify whether this dual pattern reflects coincidental findings or a broader, multi-level immune dysregulation affecting follicular structures in CVG patients.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication.

Footnotes

Authorship Contributions

Design: S.Y., Analysis or Interpretation: Ş.B., Literature Search: B.M.D., Writing: B.M.D.

Conflict of Interest: The authors declared that they have no conflict of interest.

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Case Report

An Unusual Presentation of Cutaneous Mucormycosis Mimicking Recalcitrant Dermatophytosis: A Case Report

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Abstract

We present the case of a 45-year-old woman who was initially diagnosed with and managed for recalcitrant tinea corporis and cruris. The patient had been treated with multiple courses of topical and systemic antifungal agents without clinical improvement. Upon further evaluation, mycological culture followed by molecular identification by sequencing of the internal transcribed spacer region confirmed Rhizopus stolonifer, a member of the Mucorales order, as the causative organism. The patient was subsequently treated with systemic posaconazole, leading to complete clinical resolution. This case underscores the importance of considering opportunistic molds like Mucorales in the differential diagnosis of chronic or treatment-resistant superficial fungal infections. It also highlights the critical role of advanced diagnostic modalities, including fungal culture and molecular methods, for accurate pathogen identification and appropriate antifungal therapy.

Keywords: Cutaneous mucormycosis, antifungal agents, polymerase chain reaction, Rhizopus infections, molecular diagnosis

Introduction

The global incidence of cutaneous fungal infections is rising, accompanied by a concerning decrease in clinical responsiveness to conventional antifungal therapies, leading to an increase in difficult-to-treat cases.[1] Accurate identification of the causative pathogen is crucial for effective management, especially when standard treatments fail. We present a case initially treated as recalcitrant tinea corporis and cruris, where further investigation revealed cutaneous mucormycosis caused by Rhizopus stolonifer. This report emphasizes the utility of advanced diagnostic methods and targeted therapy for managing complex fungal infections.

Case Report

A 45-year-old female with a history of hypertension and otherwise healthy, presented to our dermatology clinic with a two-year history of persistent and newly emerging skin lesions clinically suggestive of tinea corporis and cruris. Previous intermittent treatment over two years with oral itraconazole, followed by a one-month course of oral fluconazole (100 mg twice daily), and various topical combination therapies yielded no improvement. Dermatological examination revealed sharply demarcated annular erythematous plaques on the dorsal aspect of the right hand, the bilateral gluteal and intergluteal areas, the medial aspect of the left thigh, and the inframammary regions. No family history of similar symptoms or related conditions was noted.

The initial diagnostic evaluation included microscopic examination of skin scrapings using potassium hydroxide preparation, which revealed hyphal structures, supporting a clinical diagnosis of fungal infection. Subsequently, a tissue biopsy sample from a representative lesion was obtained for a

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detailed microbiological analysis. The sample was cultured on sabouraud dextrose agar (SDA; Hampshire, United Kingdom) and incubated at 37 °C. Rapidly expanding mycelial growth was observed within 48 h (Figure 1). Microscopic examination of the pure culture using the cellophane tape method stained with lactophenol cotton blue revealed morphological features consistent with the Mucorales order (Figure 1). For definitive identification, sequencing of the 18S ribosomal DNA (rDNA) and internal transcribed spacer (ITS) regions (ITS1, ITS4) was performed, which identified the isolate as Rhizopus stolonifer (Figure 2).

Following consultation with the Infectious Diseases Department, systemic antifungal therapy targeting Mucorales was initiated. The patient received posaconazole at a loading dose of 300 mg twice daily for one day, followed by a maintenance dose of 300 mg once daily. After six months of posaconazole therapy, complete regression of the lesions was observed. The most persistent lesion in the gluteal area showed only residual post-inflammatory hyperpigmentation (Figure 3). Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

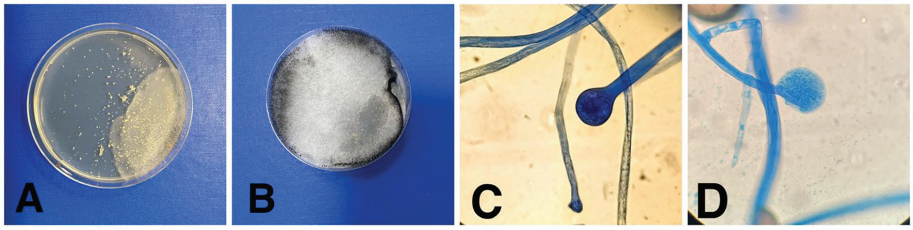

Figure 1. Petri dish, surface side, the colony was initially white (24th hour) (A), but subsequently turned gray and black (5th day) (B), in lactophenol blue staining at x 40 magnification septal hyphal tick structures, sporangium, sporangiophore, columella sporangiospore structures are observed (C, D)

Figure 2. Agarose gel images of ITS PCR products of culture sample number 1
ITS: Internal transcribed spacer, PCR: Polymerase chain reaction

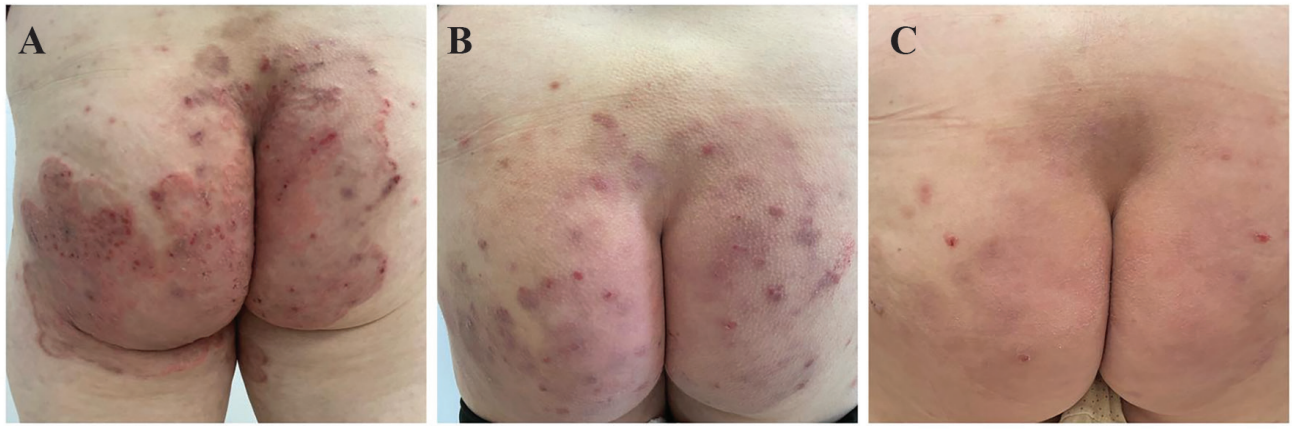

Figure 3. (A) Before start treatment (B) 3rd month of posaconazole treatment (C) 6th month of posaconazole treatment

Discussion

Cutaneous mucormycosis represents the third most common clinical form of mucormycosis. While often associated with underlying conditions such as diabetes mellitus and hematological malignancies, a significant proportion of cases (approximately 39.6%) occur in individuals with no apparent predisposing factors. Although the presence of a black eschar is considered a hallmark clinical feature of mucormycosis, it is not universally observed in all cases. In many cases, including ours, the initial presentation may be atypical and lack this classical finding.[2] Clinical diagnosis requires laboratory confirmation. Identifying fungi belonging to the order Mucorales based solely on colony and microscopic morphology can be challenging because of overlapping characteristics among different species. Advanced molecular techniques, such as polymerase chain reaction and sequencing, particularly targeting the ITS region, currently provide the most accurate means of species-level identification within Mucorales.[3] These methods facilitate early and precise diagnosis, which is critical for optimizing outcomes in this potentially rapidly progressive disease.

The *in vitro* susceptibility of Mucorales to azole antifungals varies significantly among species. Posaconazole generally exhibits the most potent activity, followed by isavuconazole. Itraconazole demonstrates limited activity, whereas voriconazole is typically inactive against most Mucorales species.[4] The successful outcome in our patient treated with posaconazole aligns with these susceptibility patterns and highlights the importance of selecting an appropriate antifungal agent based on accurate pathogen identification.

This case is noteworthy because the clinical presentation closely mimicked common dermatophytosis (tinea corporis and cruris), leading to initial misdiagnosis and ineffective treatment. The lack of response to itraconazole and fluconazole, which are commonly used for dermatophytes, should prompt the consideration of alternative fungal pathogens, including opportunistic molds.

Conclusion

This report describes an unusual case in which Rhizopus stolonifer, a member of the Mucorales order, caused a cutaneous infection clinically resembling recalcitrant tinea. This case underscores the critical importance of mycological culture and molecular identification methods in diagnosing superficial fungal infections that are refractory to standard antifungal therapies. Accurate pathogen identification allowed for targeted treatment with posaconazole, leading to complete clinical resolution. Clinicians should maintain a high index of suspicion for uncommon fungal pathogens, including Mucorales, in cases of persistent or treatment-resistant cutaneous fungal diseases.

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.U., H.S.Ç., Concept: S.A.T., Design: S.A., S.A.T., Data Collection or Processing: S.A., Analysis or Interpretation: S.A., Literature Search: S.A., S.A.T., Writing: G.A., A.T. S.A., S.A.T., S.U., H.S.Ç.

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